SEP 29 2004

IPW 1639

OIPE JC24
SEP 28 2004
PATENT & TRADEMARK OFFICE

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*ADMITTED IN NEW JERSEY ONLY
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September 22, 2004

VIA PRIORITY MAIL
Alan Koller, Ph.D., Esq.
Sr. Assistant General Counsel
Purdue Pharma LP
One Stamford Forum
Stamford, CT 06901

Re: U.S. Patent Application No. 10/057,630
Entitled: **ANALGESIC COMBINATION OF OXYCODONE AND NIMESULIDE**
Euro-Celtique, S.A.
Your Ref.: PTO176
Our Ref. No.: 200.1079CON5

Dear Alan:

We have now received an Office Action for the above-referenced patent application, a copy of which along with related papers are enclosed for your review.

A response to the Office Action is due **December 7, 2004**, although extensions of time are obtainable if necessary.

Absent your instructions to the contrary, we shall prepare a draft response for your review and consideration prior to the due date. On the other hand, if you have any comments or suggestions concerning this Office Action, we look forward to receiving the same.

Very truly yours,

Clifford M. Davidson

CMD:ie
Enclosure

cc: Robert J. Paradiso, Esq.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,630	01/25/2002	Ronald M. Burch	200.1079CON5	3300

7590 09/07/2004

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

EXCEL 9-10-04
IPM 9-10-04
3-7-05 Office Action Response Due (Deadline Date)
12-7-04 Office Action Response Due (3 Month Date)
11-7-04 Reminder
10-7-04 Send Reporting Letter
CMD/RJP/RVZ

PTO-90C (Rev. 10/03)

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Office Action Summary	Application No.	Applicant(s)	
	10/057,630	BURCH ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-44,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/02; 1/25/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 38-44 and 46-47 are currently pending and under consideration..

Election/Restriction

1. Applicant's election without traverse of Group II (claims 38-44 and 46-47; use in methods of treating pain using oxycodone and nimesulide) in the correspondence dated 6/14/04 is acknowledged.

Priority

Applicant should update the cross-reference to parent application which has subsequently issued as a patent.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 37-41, 43-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86), Swingle et al. Drugs Exptl. Clin. Res. Vol. X(8-9) (1984) pages 587-597 and/or Rabasseda. Drugs of Today Vol. 32, No. 5 (1996) pages 365-384.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. a non-steroidal anti-inflammatory drug or NSAID (preferably ibuprofen: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47: See col. 2)

with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46).

The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a "single dosage form" (e.g. see col. 3-8: and present claim 40) or sequentially administered (e.g. as in present claim 42; see i.e. col. 8-9 ; ".. mice are dosed sequentially..."). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic "i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components",

thereby permitting "reduced dosages of narcotic analgesics" (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components" resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32 (e.g. compare to present 43 and 44 "reduced" active ingredients). Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of nimesulide for ibuprofen, or alternatively, the further incorporation of (e.g. encompassed by "consisting essentially of") Nimesulide into the Baker compositions.

Swingle et al. teach that Nimesulide is a sulfoanilide non-steroidal anti-inflammatory drug (e.g. NSAID) that is four times more potent that indomethacin in anti-inflammatory rodent assays and as compared to other NSAID's (including ibuprofen), nimesulide has an extremely favourable therapeutic ratio in rats and has minimal GI toxixity in rats and pigs. See e.g. Abstract; Figures 2-11.

Similarly, Rabasseda teach that Nimesulide is a sulfonanilide NSAID that possess potent antiinflammatory, analgesic and antipyretic activites in a wide-range of

animal experimental models and a potent and specific inhibitor of cyclooxygenase (e.g.COX2) and as such has a much lower risk of gastroduodenal lesions in comparison with other NSAID's, including ibuprofen. E.g. see pages 365 and 374-377.

Accordingly, one of ordinary skill in the art would have been motivated to substitute Nimesulide (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Swingle et al. and/or Rabasseda reference teachings that Nimesulide is more efficacious, and safer with less side effects (e.g. as compared to other non-selective COX-2 inhibitor NSAID's i.e. ibuprofen).

Alternatively, one of ordinary skill in the art would have been motivated to incorporate Nimesulide, with its potent analgesia and reduced side-effect, into the Baker ibuprofen/oxycodone compositions in order to reduce the amounts (e.g. therapeutic/subtherapeutic) of ibuprofen/oxycodone in order to avoid the side effects (e.g addiction) or toxicity resulting from ibuprofen/oxycodone.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID Nimesulide (for the NSAID ibuprofen) or supplement Baker's composition with Nimesulide in light of the benefits of Nimesulide (increased

safety/decreased side effect as compared to ibuprofen) as taught by the Swingle et al. and/or Rabasseda references.

4. Claims 38-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Baker et al. '937, Swingle et al. and/or Rabasseda references. references applied to claims 37-41, 43-44 and 46-47 above, and further in view of Mayer et al. US Pat. No. 5834,479 (11/98).

The teaching of the Baker, Swingle and/or Rabasseda references recited above is hereby incorporated by reference in its entirety.

To the extent that the Baker, Swingle and/or Rabasseda references fail to teach the administration of the analgesia active agent (e.g. Nimesulide) "before, ... with, or after" administration of the oxycodone" (particularly before/after) (e.g. see present claim 41) the Mayer et al. reference is cited.

The Mayer et al. reference teaches that analgesia effectiveness of an analgesia active agent (e.g. a NSAID, such as ibuprofen see i.e. table in col. 7) can be "significantly enhanced" by administering (e.g. oral administration) the active agent "prior to, with or following the administration of an analgesia enhancer" (e.g. a nontoxic NMDA receptor blocker and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation) such as "dextromethorphan", which is the D-isomer of codeine . See e.g. col. 1; patent claims.

Accordingly, the Mayer et al. reference provides motivation to one of ordinary skill in the art to not only co- administer different analgesic agents to achieve enhanced

analgesia, but to also administer the NSAID prior or subsequent to the second analgesic agent i.e. an analgesia enhancer, which includes codeine or its derivatives (e.g. dextromethorphan, dextrorphan, oxycodone etc.) .

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the combined Baker, Swingle and/or Rabasseda reference teachings by administering one of the analgesic active agents (e.g. Nimesulide) "before, ... with, or after" administration of the second analgesic agent (e.g. oxycodone) in order to obtain significantly enhanced analgesia.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
August 26, 2004

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JC24

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON5	SERIAL NO.: Not yet known 10/057,630
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: Herewith	GROUP: Not Yet Known 1639

J1060 U.S. PTO 10/057630 09/28/04

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5 8 5 9 2 5 7	01/12/99	Talley	548	247	08/14/98
	AB	5 8 6 3 9 2 2	01/26/99	Mayer, et al.	514	270	07/02/99
	AC	5 8 4 0 7 3 1	11/24/98	Mayer, et al.	514	289	08/02/95
	AD	5 8 6 9 4 9 8	02/09/99	Mayer, et al.	514	282	07/07/97
	AE	5 8 6 1 4 1 9	01/19/99	Dube, et al.	514	334	07/11/97
	AF	5 7 8 9 4 1 3	08/04/98	Black, et al.	514	255	01/21/97
	AG	5 6 0 4 2 6 0	02/18/97	Guay, et al.	514	605	11/04/93
	AH	5 4 5 8 8 7 9	10/17/95	Singh, et al.	424	400	09/30/94
	AI	5 5 1 6 8 0 3	05/14/96	Raffa	514	570	03/01/95
	AJ	5 8 4 3 4 6 8	12/01/98	Burkoth, et al.	424	448	05//13/96

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK	Differential Inhibition of Cyclooxygenase-1 (COX-1) and -2 (COX) By NSAIDS: Consequences on Anti-Inflammatory Activity Versus Gastric and Renal Safety, M. Pairet, et al., Inflammopharmacology 4; 61-70, (1996).
	AL	Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation, Derek W. Gilroy, et al. European J. Pharm 355 pp 211-217, (1998).
	AM	Cyclooxygenases 1 and 2, J.R. Vane, et al. Annu. Rev. Pharmacol. Toxicol. 38: 97-121, (1998).
	AN	Analysis of the effects of cyclooxygenase (COX)-1 and COX-2 in spinal nociceptive transmission using indomethacin, a non-selective COX inhibitor, and NS-398, a COX-2 selective inhibitor, Tatsuo Yamamoto, et al. Brain Research 739:104-110, (1996)
	AO	Comparative Analgesic Efficacy of Nimesulide and Diclofenac Gels after Topical Application on the Skin, S. Sengupta, et al., Skin Pharmacol. And Applied Skin Phys. 11:273-278, (1998).
	AP	Carrageenan-induced hyperalgesia is associated with increased cyclo-oxygenase-2 expression in spinal cord, Cartiona Hay and Jacqueline de Belleroche, Neuro Report 8, 1249-1251, (1997).
	AQ	The Mechanisms of Action of NSAIDs in Analgesia, Jeremy N. Cashman, Drugs 52 Supp. 5:13-23, (1996).
	AR	Differential effects of inhibition of isoforms of cyclooxygenase (COX-1, COX-2) in chronic inflammation, D.W. Gilroy, et al. Inflamm. Res. 47:79-85, (1998).
	AS	Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for Selective Inhibition and Progress to Date, Don E. Griswold and Jerry L. Adams, Medicinal Research Reviews, Vol. 16, No. 2, pp. 181-208, (1996).

EXAMINER	DATE CONSIDERED
	8/26/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON5	SERIAL NO.: Not Yet Known 10/057,630
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U.S. PATENT DOCUMENTS

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	BA						
	BB						
	BC						
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	BJ						
	BK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	BM	Cyclooxygenase in biology and disease, Raymond N. Dubois, et al., FASEB J. Vol. 12 pp. 1063-1073 (1998).
	BN	Pharmacology of Meloxicam, A new Non-Steroidal Anti-Inflammatory Drug With An Improved Safety Profile Through Preferential Inhibition of COX-2, G. Engelhardt, British J. Rheumatology, 35 (supp 1):4-12, (1996)
	BO	Cyclooxygenase 1 Contributes to Inflammatory Responses in Rats and Mice: Implications for Gastrointestinal Toxicity, John L. Wallace, et al. Gastroenterology, 115:101-109 (1998).
	BP	Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: possible physiological and therapeutic implications, M. Pairet and G. Engelhardt, Fundam. Clin. Pharmacol. 10:1-15, (1996).
	BQ	Involvement of Prostaglandins Produced by Cyclooxygenase-1 in Murine Viscernonociception Induced by Phenylquinone, Hidenobu Kusuhara, et al. Prostaglandins 55: 43-49, (1998).
	BR	Effect of COX-1 and COX-2 Inhibition on Induction and Maintenance of Carrageenan-Evoked Thermal Hyperalgesia in Rats, D. Dirig, et al. J. Pharmacol. And Experimental Therapeutics Vol. 285, No. 3, pp 1031-1038.

EXAMINER	DATE CONSIDERED
	3/26/04

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	CA						
	CB						
	CC						
	CD						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	CE	9 9 0 7 4 1 3	2/18/99	WO				
	CF	9 9 3 2 1 1 9	7/1/99	WO				
	CG							
	CH							
	CI							
	CJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	CK	Effect of meloxicam on postoperative pain after abdominal hysterectomy, J.P. Thompson et al. British Journal of Anaesthesia 84 (2) 151-4 (2000).
	CL	Intrathecal cyclooxygenase inhibitor administration attenuates morphine antinociceptive tolerance in rats. C.S. Wong et al., British Journal of Anaesthesia 85 (5) 747-51 (2000).
	CM	Cyclooxygenase inhibitors increase morphine effects on mesolimbic dopamine neurons, M. Melis, et al. Eur. J. Pharmacology 387 (1) R1-R3 (2000).
	CN	Synergistic antiallodynic effects of spinal morphine with ketorolac and selective COX-1 and COX -2 inhibitors in nerve-injured rats, J.M. Lashbrook, et al. Pain 82 (1) 65-72 (1999).
	CO	Enhancement of opioid inhibition of gaba-ergic synaptic transmission by cyclo-oxygenase inhibitors in rat periaqueductal grey neurones, Vaughn et al. British Journal of Pharmacology 123 (8) 1479-81 (1998).

EXAMINER	DATE CONSIDERED
	8/26/04

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	DA	5 4 7 4 9 9 5	12/12/95	Ducharme et al.	514	241	01/10/94
	DB	5 6 9 1 3 7 4	11/25/97	Black et al.	514	473	05/18/95
	DC						
	DD						
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FOREIGN PATENT DOCUMENTS

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	DL							
	DM							
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	DO							
	DP							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	DQ	
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	DS	

EXAMINER	DATE CONSIDERED
	8/20/04

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	EA	3 8 0 0 0 4 1	03/26/74	Miller, et al.	424	273	03/02/71
	EB	4 3 2 2 4 2 7	03/30/82	Buyinski, et al.	424	260	04/16/81
	EC	4 3 3 8 3 2 4	08/06/82	Gardocki	424	266	03/17/81
	ED	4 4 0 4 2 1 0	09/13/83	Schmidt	424	260	06/30/82
	EE	4 4 0 7 8 0 4	10/04/83	Schmidt	424	260	06/30/82
	EF	4 4 0 7 8 0 5	10/04/83	Schmidt	424	260	06/30/82
	EG	4 4 6 4 3 7 6	08/07/84	Sunshine, et al.	424	253	10/11/83
	EH	4 4 8 6 4 3 6	12/04/84	Sunshine, et al.	424	253	03/11/83
	EI	4 4 8 8 0 8 0	12/18/84	Lomen	424	260	12/06/82

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	EJ	2 0 2 3 3 4 9	02/18/91	Canada	A61K	31/44		
	EK	0 2 7 4 8 4 5	07/20/88	EP (A1)	A61K	31/19		
	EL	0 3 8 8 1 2 5	09/19/90	EP (A1)	A61K	31/485		

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	EM	Pharmacokinetics and Drug Input Characteristics for a Diclofenac-Codeine Phosphate Combination Following Oral and Rectal Administration A. Hansen, et al. Arzneim-Forsch./Drug Res. 48 (I) 57-63 (1996).
	EN	Comparison of a Standard Ibuprofen Treatment Regimen with a New Ibuprofen/Paracetamol/Codeine Combination in Chronic Osteo-arthritis G.K. Vlok, et al. Univ. Stellenbosch and Tygerberg Hospital, Dept. Orthopaedic Surg. pp 3-6, (1987).
	EO	
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EXAMINER	DATE CONSIDERED
	8/24/04

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FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1078CON5	SERIAL NO.: Not Yet Known 10/057,630
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: Not Yet Known	GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MC	FA	4 5 6 7 1 8 3	01/28/86	Sunshine, et al.	514	264	12/12/83
	FB	4 5 6 9 9 3 7	02/11/86	Baker, et al.	514	282	02/11/83
	FC	4 5 7 1 4 0 0	02/18/86	Arnold	514	282	12/18/84
	FD	4 5 8 7 2 5 2	05/06/86	Arnold	514	282	12/18/84
	FE	4 6 1 9 9 3 4	12/28/88	Sunshine, et al.	514	277	07/08/85
	FF	4 8 9 0 9 2 7	09/01/87	Voss, et al.	514	282	02/03/86
	FG	4 8 3 9 1 7 6	06/13/89	Pahkhania, et al.	424	465	12/08/87
	FH	4 8 4 4 9 0 7	07/04/89	Elger, et al.	424	465	08/14/86
	FI	4 9 2 7 8 5 4	05/22/90	Sunshine, et al.	514	570	08/21/89
	FJ	5 1 6 4 3 9 8	12/17/92	Sims ,et al.	514	282	04/01/91
	FK	5 1 9 0 9 4 7	03/02/93	Riess, et al.	514	282	08/16/91
MC	FL	5 2 4 0 6 9 4	08/31/93	Gwaltney, Jr.	424	45	12/19/91

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
MC	FM	0 0 6 8 8 3 8	06/25/82	EP (A1)	A61K	31/485		
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		FILING DATE: Not Yet Known	GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

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ML	GA	5 4 0 9 9 4 4	04/25/95	Black, et al.	514	359	03/12/93
	GB	5 4 3 8 2 6 5	08/25/95	Black, et al.	514	420	11/12/93
	GC	5 5 1 0 3 6 8	04/23/96	Lau, et al.	514	419	05/22/95
	GD	5 5 2 1 2 1 3	05/28/96	Prasit, et al.	514	443	08/29/94
	GE	5 5 5 0 1 4 2	08/27/96	Ducharme et al.	514	365	05/08/95
	GF	5 5 5 2 4 2 2	09/03/96	Gauthier, et al.	514	368	01/11/95
	GG	5 6 0 4 2 5 3	02/18/97	Lau, et al.	514	415	05/22/95
MM	GH	5 6 3 9 7 8 0	06/17/97	Lau, et al.	514	419	05/22/95

FOREIGN PATENT DOCUMENTS

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	GI							
	GJ							
	GK							
	GL							
	GM							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	GN	Anti-inflammatory Drugs and Their Mechanism of Action J.R. Vane, et al. Inflamm. Ress. 47, Supplement 2 (1998).
	GO	
	GP	
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	HL							
	HM							
	HN							
	HO							
	HP							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

mt	HQ	Rorarius et al., "Non-Steroidal Anti-Inflammatory Drugs for PostOperative Pain Relief." Curr. Opin. In Anaesthesiology, 7, 358-362). (1994)
	HR	Hanses et al. "Pharmacokinetics and Drug input Characteristics for a Diclofenac-Codeine Phosphate Combination Following Oral and Rectal Administration," Arzneim.-Forsch./Drug Res., 46(I), Nr. 1,57-63. (1996)
	HS	Merck Index, Twelfth Edition, Merck & Co. Publishers, page 1194. (1996)
mt	HT	Goodman and Gillman's: Pharmaceutical Basis of Therapeutics, "Chapter 22: Opioid Analgesics and Antagonists", MacMillan Publishing Co., Inc., pp-494-497, esp. Table 22-1, p. 496. (1980)

EXAMINER	DATE CONSIDERED
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APPLICANT(S): Ronald M. BURCH, et al.	
FILING DATE: September 17, 1998	GROUP: ~~1627~~ 1639

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AA	0 6 5 4 2 6 3	05/24/95	EP (A1)	A61K	31/135		
	AB	0 6 5 4 2 6 3	05/24/95	EP (B1)	A61K	31/135		
	AC	9 7 1 7 9 7 8	05/22/97	WO	A61K	33/00		
	AD	9 7 2 5 9 8 8	07/24/97	WO	A61K	31/495		
	AE	9 7 3 2 8 5 7	09/12/97	WO	C07D	241/104		

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

AF	Dray et al. New Pharmacological Strategies for Pain Relief. Annual Review of Pharmacology & Toxicology, 36, pp. 253-280. (1996).
AG	Brasseur, L. Revue des therapeutiques pharmacolgolques actuelles de la douleur. Drugs, 53 Suppl 2, pp. 10-17. (1997)
AH	Rang et al. New molecules in analgesia. British Journal of Anesthesia, 75, pp. 145-156 (1995)
AI	Beaver, WT. Combination Analgesics. American Journal of Medicine, 77 (Suppl 3A), pp. 38-53. (1984).
AJ	Beaver, WT. Chapter 29: Nonsteroidal Antiinflammatory Analgesics and Their Combinations with Opioids. In Evaluation and Treatment of Chronic Pain, 2nd ed., William & Wilkins pp. 363-383. (1992).
AK	Goodman & Gilman's. The Pharmacological Basis of Therapeutics, 9th Edition. McGraw-Hill, New York, pp 535 and 551-552.
AL	Picard et al. Ketorolac potentiates morphine in postoperative patient-controlled analgesia. Pain, 73, 3 pp. 401-406. (1997).
AM	Etches et al. Continuous Intravenous Administration of Ketorolac Reduces Pain and Morphine Consumption After Total Hip or Knee Arthroplasty. Anesthesia & Analgesia, 81 (6), pp. 1175-1180. (1995).
AN	Hodsman et al. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia, 42(9), pp. 1005-1008. (1987).
AO	Kaasalainer et al. Developments in the treatment of cancer pain in Finland: The third nation-wide survey. Pain, 70, 2-3, pp. 175-183. (1997).
AP	Sunshine et al. Analgesic Efficacy of a Hydrocodone with Ibuprofen Combination Compared with Ibuprofen Alone for the Treatment of Acute Postoperative Pain. Journal of Clinical Pharmacolology, 37 (10), pp. 908-915. (1997).
AQ	Insel. Chapter 27: Analgesic-Antipyretic and Anti-Inflammatory Agents. In Hardman, ed., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition. McGraw-Hill, New York, pp. 654-655. (1996).
AR	Polisson. Non-steroidal Anti-Inflammatory Drugs: Practical and Theoretical Consideration in Their Selection. The American Journal of Medicine, 100 (Suppl 2A), pp. 2A-31S - 2A-36S. (1996).
AS	Vane, J. Towards a better aspirin. Nature, 367, pp. 215-216. (1994).
AT	Simon, L.S. Nonsteroidal Antiinflammatory Drugs and Their Effects: The Importance of COX 'Selectivity'. Journal of Clinical Rheumatology, 2 (3), pp. 135-140. (1996).

EXAMINER _____ DATE CONSIDERED 8/26/04

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	LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: September 17, 1998	GROUP: ~~1627~~ 1639

USPTO PATENT & TRADEMARK OFFICE DEC 02 2002

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	BA	Van Ryn et al. Selective cyclooxygenase-2 inhibitors: pharmacology, clinical effects, and therapeutic potential. Expert Opinion On Investigational Drugs. pp. 609-614. (1997).
	BB	Vane et al. New insights into the mode of action of anti-inflammatory drugs. Inflammation Research. 44, (No.1), pp 1-10 (1995).
	BC	Engelhardt. Meloxicam: A Preferential Inhibitor of COX-2. British Journal of Rheumatology. 34, Abstract Suppl. 1, p. 48. (1995). Abstract.
	BD	Lane, N.E. Pain Management in Osteoarthritis: The Role of COX-2 Inhibitors. Journal of Rheumatology. Vol. 24, Suppl 49, pp. 20-24. (1997).
	BE	Boyce et al. L-745,337: A Selective Inhibitor of Cyclooxygenase-2 Elicits Antinociception But Not Gastric Ulceration In Rats. Neuropharmacology Vol. 33, pp. 1609-1611. (1994).
	BF	Donelly et al. COX-II Inhibitors - a new generation of safer NSAIDS? Alimentary Pharmacology and Therapeutics, 11, 2, pp. 227-236. (1997).
	BG	Wallace, J.L. Nonsteroidal Anti-inflammatory Drugs and Gastroenteropathy: The Second Hundred Years. Gastroenterology, 112, 3, pp. 1000-1016. (1997).
	BH	Robinson, D.R. Regulation of Prostaglandin Synthesis by Antiinflammatory Drugs. J Rheumatology, 24, Suppl. 47, pp. 32-39. (1997).
	BI	Tannenbaum et al. An Evidence-Based Approach to Prescribing NSAIDS in Muscoskeletal Disease: A Canadian Consensus. Canadian Medical Association Journal, 155, 1, pp. 77-88. (1996).
	BJ	Mehlisch et al. Analgesic Efficacy and Plasma Levels of a Highly Selective Inhibitor of COX-2 (SC-58635, SC) in Patients with Postsurgical Dental Pain. Journal of Clinical Pharmacology, 37, 9, 863. (1997). Abstract.
	BK	Dammann. Selective COX-2 Inhibition: Its Relevance for NSAID-Gastrointesinal Toxicity. Gut, 39, Suppl. 3, A151. (1996). Abstract.
	BL	Penning et al. Synthesis and Biological Evaluation of the 1, 5 -diarylpyrazole class of cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib). Journal Of Medicinal Chemistry, 40(9), 1347-65. (1997).
	BM	Lipsky et al. Outcome of Specific COX-2 Inhibition In Rheumatoid Arthritis. Journal Of Rheumatology, 24 Suppl 49, pp. 9-14. (1997).
	BN	
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RECEIVED DEC 04 TECH CENTER 1600/2900

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LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: September 17, 1998	GROUP: ~~1627~~ 1634

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U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
AM	AH	07342754	11/04/1997	Australia	C07D	261/08		
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OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

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Notice of References Cited	Application/Control No. 10/057,630	Applicant(s)/Patent Under Reexamination BURCH ET AL.	
	Examiner Bennett Celsa	Art Unit 1639	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-5,834,479	11-1998	Mayer et al.	514/289
	B	US-			
	C	US-			
	D	US-			
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FOREIGN PATENT DOCUMENTS

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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Swingle et al. Drugs Exptl. Clin. Res. Vol. X(8-9) (1984) pages 587-597
	V	Rabasseda. Drugs of Today Vol. 32, No. 5 (1996) pages 365-384.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DRUGS EXPTL. CLIN. RES. X(8-9) 587-597 (1984)

PRECLINICAL PHARMACOLOGICAL STUDIES WITH NIMESULIDE*

SWINGLE K.F., MOORE G.G.I.

Riker Laboratories, 3M-Company, Saint Paul, MN, USA.

Summary: *Nimesulide is a new nonsteroidal anti-inflammatory drug (NSAID) which is chemically different from other drugs of this class because its functional acidic group is sulfonanilide. It has three to four times the potency of indomethacin in conventional anti-inflammatory assays in rodents. It possesses analgesic and antipyretic activities. Compared with other NSAIDs nimesulide has an extremely favourable therapeutic ratio in rats and has minimal acute gastrointestinal toxicity in rats and pigs. Its relatively weak inhibition of prostaglandin synthetase* in vitro *suggests that the molecule is either activated* in vivo *or possesses additional mechanisms of anti-inflammatory action. The unique potency conferred on the molecule by the 4-nitro substituent leads the authors to speculate that metabolic activation involves reduction of this group.*

Introduction

Most of the currently available acidic, non-steroidal anti-inflammatory drugs are either carboxylic acids (e.g., indomethacin, naproxen, ibuprofen) or enolic acids (e.g., phenylbutazone, sudoxicam). Nimesulide (4-nitro-2-phenoxymethanesulfonanilide) is a potent anti-inflammatory compound whose functional acidic group is sulfonanilide. Nimesulide was selected from a group of several hundred sulfonalides synthesized at Riker Laboratories as the most potent anti-inflammatory compound of the series (1, 2).

The authors had previously conducted preliminary safety and anti-inflammatory/analgesic efficacy studies in humans with another sulfonanilide, diflumidone (Fig. 1).

Methods and results

Anti-inflammatory activity (3, 4)

Carrageenan-induced oedema of the rat's paw. The method described by Winter *et al.* (5) was used, with slight modifications. Drugs were administered 15 min before, and the amount of swelling of the rat's hind paw determined 3 h after, the subplantar injection of a 0.5% suspension of car-

* Presented at the 1st World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, Venice, 16-18 April 1984.

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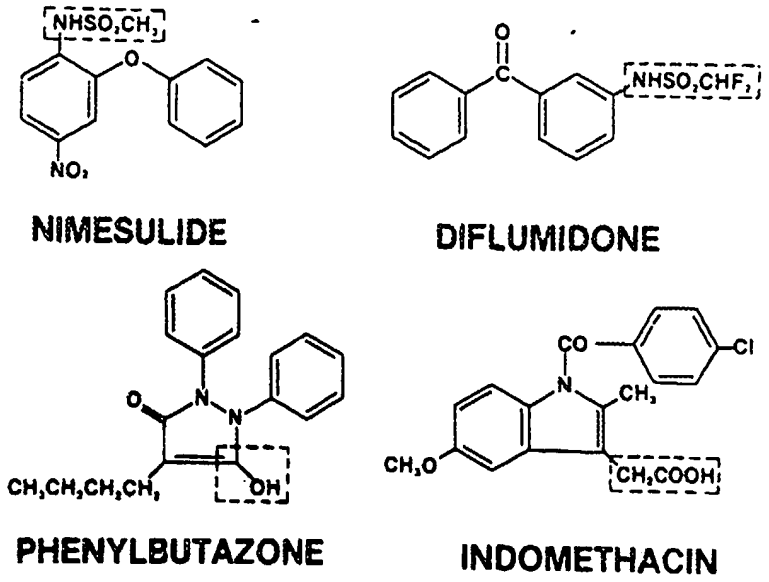

Fig. 1 Functional acidic groups of anti-inflammatory drugs.

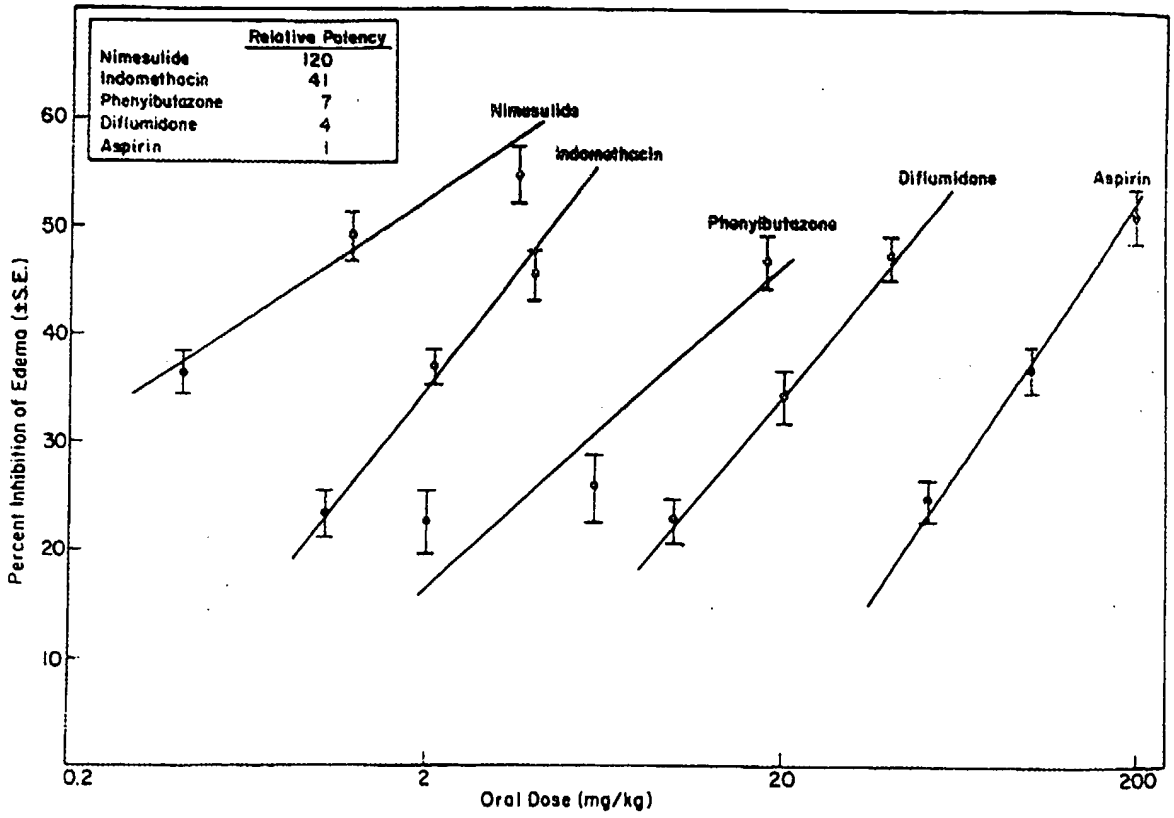

Fig. 2 Effect of nonsteroidal anti-inflammatory drugs on carrageenan-induced oedema of the rat's paw.

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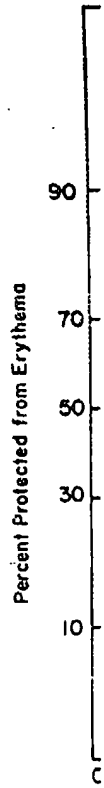

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rageenan. After oral administration, the potency of nimesulide was estimated to be approximately 120 times that of aspirin and three times that of indomethacin in this assay (Fig. 2).

Ultraviolet light-induced rythema of guinea pig skin. The method of Winter *et al.* (6) was used, with minor modifications. Drugs were administered orally 30 min before exposure of circumscribed regions of depilated skin to ultraviolet light. The erythemas were scored 2 h after exposure. The ED-50 values determined for nimesulide, indomethacin, diflumidone and aspirin are shown in Fig. 3. Nimesulide had approximately four times the potency of indomethacin in this assay.

Adjuvant-induced arthritis of the rat. Arthritis was induced in rats by the intracutaneous injection into the distal half of the tail of killed *Mycobacterium butyricum*, suspended in 0.05 ml of mineral oil (7). Drugs were administered orally after the arthritis was fully established. The minimally effective dose of nimesulide in this assay was about 0.2 mg/kg (Fig. 4).

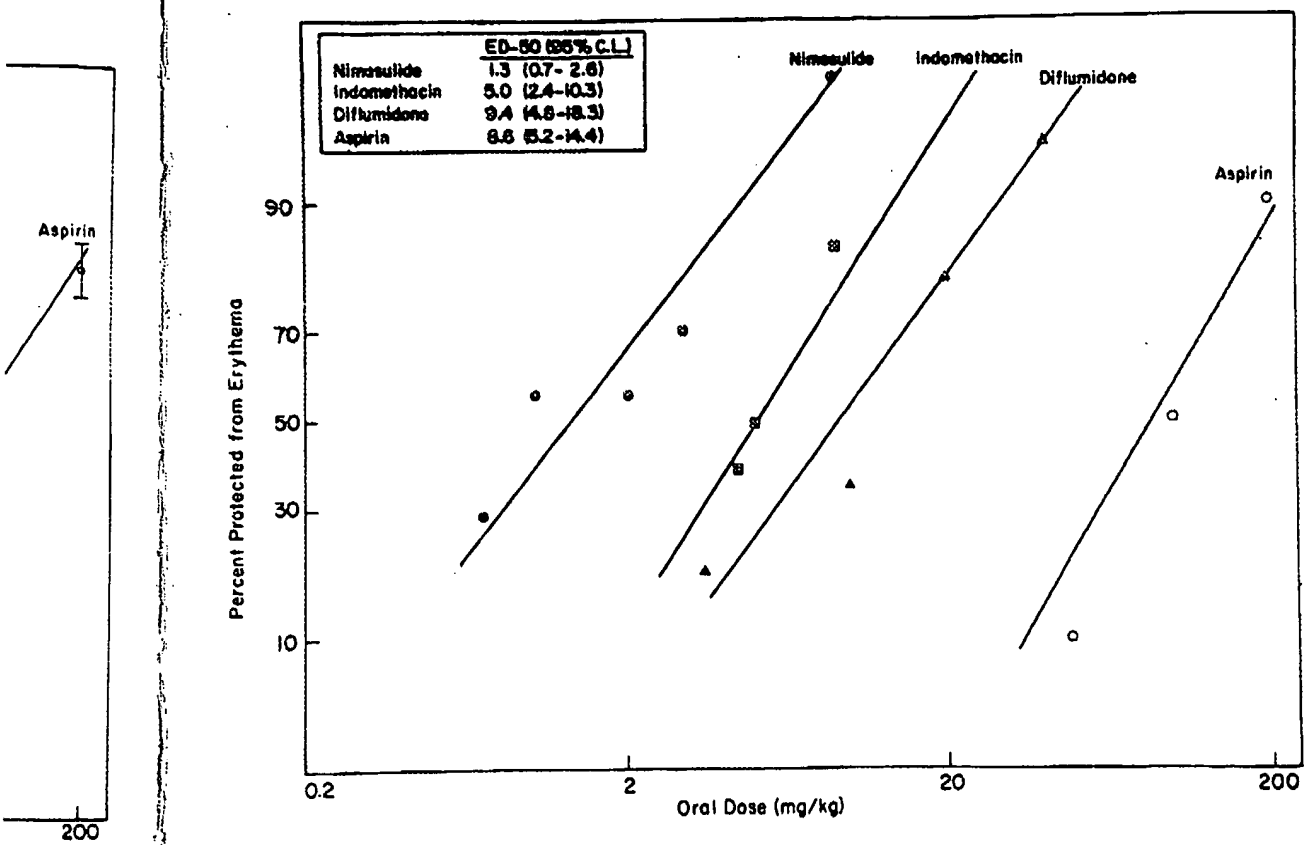

Fig. 3 Effect of nonsteroidal anti-inflammatory drugs on UV-induced erythema in guinea pigs.

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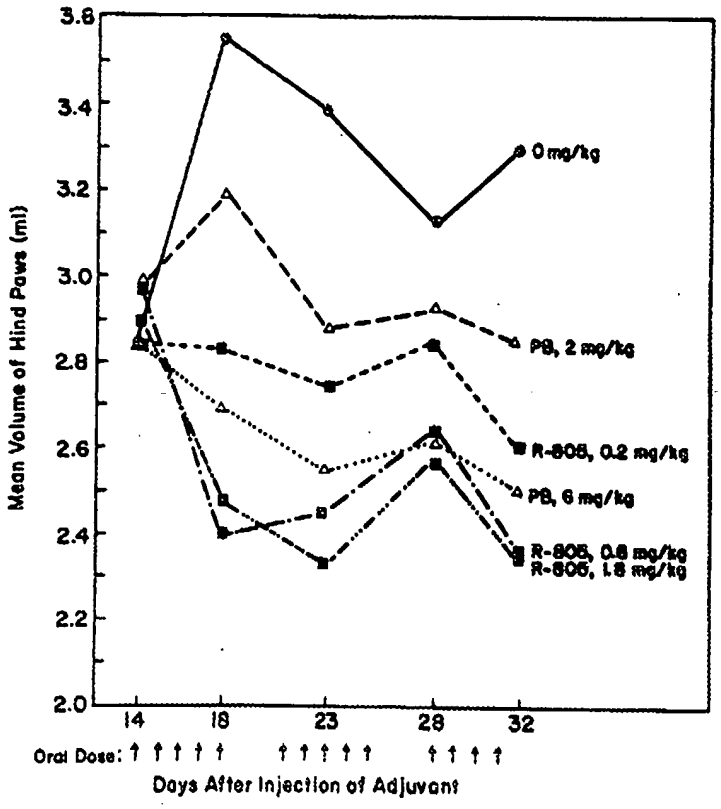

Fig. 4 Effect of nimesulide (R-805) and phenylbutazone (PB) on adjuvant-induced arthritis of the rat (Swingle *et al.* (4)).

Anti-inflammatory activity in adrenalectomized rats. The anti-inflammatory activity of nimesulide, as assessed in carrageenan-induced oedema of the rat's paw, was not affected by adrenalectomy (Fig. 5), which suggests that the drug does not produce its anti-inflammatory effects indirectly through stimulation of adrenocortical secretion.

Analgesic and antipyretic activities (8, 9)

The Randall-Selitto assay (10), as modified by Swingle *et al.* (8), determines the reaction threshold to pressure of the yeast-inflamed rat's paw. Drugs were administered orally 2 h after the injection of the yeast. Thirty minutes later the reaction thresholds to pressure of the paws were determined. The oral ED-50 of nimesulide was determined to be 5.2 (4.8-5.6) mg/kg in this assay. This is about 25 times the potency of aspirin and five times that of propoxyphene (Fig. 6).

Nimesulide was also effective in reducing the abdominal constriction response ("writhing") of mice induced by the intraperitoneal injection of phenylquinone. The drug produced 50% inhibition

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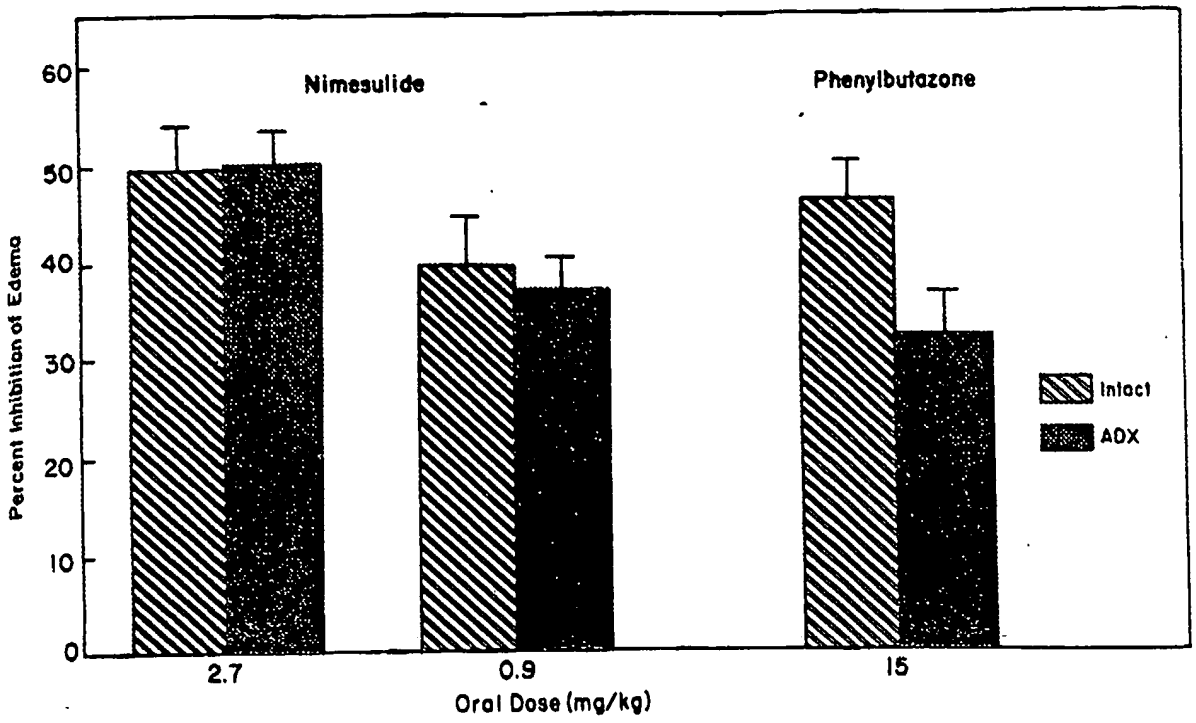

Fig. 5 Effect of adrenalectomy (ADX) on anti-oedema activity of nimesulide in the rat.

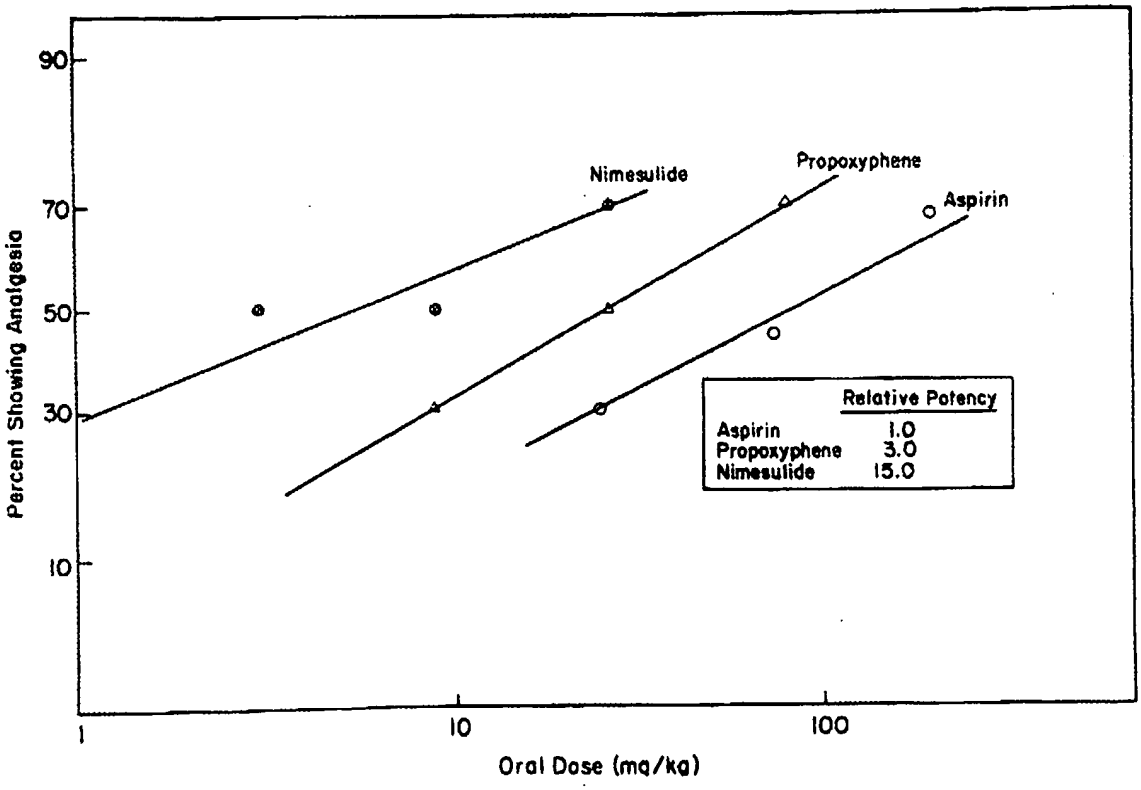

Fig. 6 Effect of analgesic drugs on reaction threshold to pressure of the inflamed rat paw.

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of the response at an oral dose of 5 mg/kg. It was estimated to have about five times the potency of aspirin in this assay. At oral doses of 1.0 to 30 mg/kg, nimesulide significantly reduced the hyperthermia induced in rats by subcutaneous injection of yeast. It was more potent than phenylbutazone as an antipyretic in this assay.

Metabolic studies (9, 11, 12)

A highly significant correlation between the mean plasma concentration and the anti-oedemic activity of nimesulide was demonstrated in the rat (Fig. 7). A plasma concentration of about 2 µg/ml resulted in 40% inhibition of carrageenan-induced oedema of the rat's paw. In man, steady state plasma levels of about 6 µg/ml are achieved with a dosage of 100 mg of nimesulide given four times a day.

Nimesulide is well absorbed after oral administration to rats, dogs or men. One metabolite (4'-hydroxynimesulide) has been positively identified

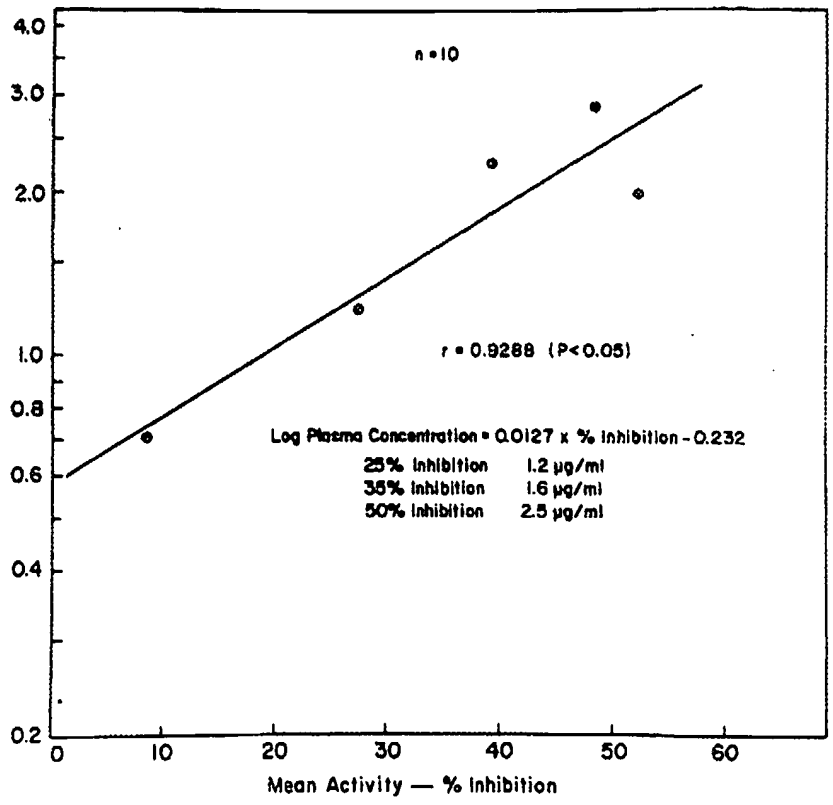

Fig. 7 Relationship between mean log plasma concentrations and mean anti-oedema activity in rats.

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in plasma from men. Excretion of nimesulide is primarily faecal in rats, suggesting the possibility of enterohepatic cycling in this species. In dogs and men both urinary and faecal routes of excretion are important. The plasma half-life for unchanged drug is about 3, 2, and 5 h for rats, dogs, and men respectively (Fig. 8).

Toxicological data

Therapeutic indices (LD-50/ED-50, oedema) were determined for nimesulide and seven other nonsteroidal anti-inflammatory drugs in rats (4) (Fig. 9). Nimesulide and naproxen possess the most favourable therapeutic indices in this species.

Rainsford (13) assessed the comparative gastric ulcerogenic activity of nonsteroidal anti-inflammatory drugs in rats. Drug effects were determined 2 h following their oral administration. Nimesulide and sulindac, among others, were classified as having low ulcerogenic activity (Fig. 10). Rainsford (unpublished data) also determined the effect of a single oral dose (100 mg/kg) of

Species	Absorption	Metabolism	Excretion	Plasma t½, Unchanged Drug
Rat	+ + +	+ +	Fecal	3 hr.
Dog	+ + +	+ +	Urinary, Fecal	2.5 hr.
Man	+ + +	+	Urinary, Fecal	4.9 hr. (2-7 hr.)

Fig. 8 Metabolic data for nimesulide.

Drug	ED_{50}, mg/kg in carrageenan assay	LD_{50}, mg/kg (95% confidence limits)	Therapeutic index (LD_{50}/ED_{50})
R-805	1.25	324 (295-356)	260
Naproxen	2.10	395 (281-557)	190
Ibuprofen	13.5	923 (833-1020)	68
Diflumidone	38.0	750 (694-811)	20
Flufenamic Acid	14.7	249 (221-280)	17
Phenylbutazone	29.5	406 (375-440)	14
Acetylsalicylic acid	135	1520 (1360-1710)	11
Indomethacin	2.95	21.0 (19.0-23.0)	7

Fig. 9 Acute oral therapeutic indices for nonsteroidal anti-inflammatory drugs in rats (Swingle *et al.* (4)).

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Relative Ulcerogenic Activity	Drug	Dose, mg/kg	Number of Lesions	Average Severity (0→+4)	Percent Incidence
Low	Nimesulide	100	1.0 ± 0.9	0.3	33
	Sulindac	20	2.7 ± 1.5	0.5	44
Intermediate	Ibuprofen	100	2.0 ± 1.3	1.0	60
	Phenylbutazone	100	3.8 ± 0.2	1.8	60
	Meclofenamic Acid	100	2.7 ± 2.1	0.7	67
	Naproxen	100	9.8 ± 4.6	1.3	75
High	Ketoprofen	100	28.8 ± 8.4	3.3	100
	Indomethacin	20	36.0 ± 12.0	2.0	100
	Aspirin	200	47.0 ± 6.5	4.0	100
	Tolmetin	100	63.0 ± 6.0	4.0	100

Fig. 10 Comparative gastric ulcerogenicity activities of nonsteroidal anti-inflammatory drugs in cold-stressed rats (data from Rainsford (13)).

nimesulide in stressed pigs. No gastric lesions were produced by the drug in this species, whereas aspirin produced a mean total lesion count of 33 ± 17.

Inhibition of prostaglandin synthetase (14)

Nimesulide inhibits competitively the synthesis of prostaglandins from bovine seminal vesicles. The order of potency, as shown by the IC-50 values, is indomethacin > diflumidone > nimesulide > aspirin (Fig. 11). Analysis of kinetic data results in inhibitory constants of 0.11 and 3.0 μM for diflumidone and nimesulide respectively. Thus the affinity of diflumidone for the enzyme compares most closely with that for indomethacin ($K_i = 0.15$ μM), while that for nimesulide compares most closely with phenylbutazone ($K_i = 2.3$ μM; data not shown). Aspirin has relatively weak affinity for the enzyme.

The sulfonanilides, nimesulide and diflumidone, do not show any correlation between their prostaglandin synthetase inhibitory potencies *in vitro* and their anti-inflammatory potencies *in vivo*. Nimesulide is considerably more potent (about 30 times) than diflumidone *in vivo* (Fig. 2) but the converse is found *in vitro* (Fig. 11). Similarly, nimesulide has about three times the potency of indomethacin *in vivo* but only one-fiftieth the potency of indomethacin *in vitro*. These data suggest mechanisms of anti-inflammatory action in addition to inhibition of prostaglandin synthesis for nimesulide; or, alternatively, metabolic activation of nimesulide *in vivo*. The relatively weak inhibition of prostaglandin synthesis by unchanged nimesulide might partially account for the reduced gastrointestinal toxicity of the drug.

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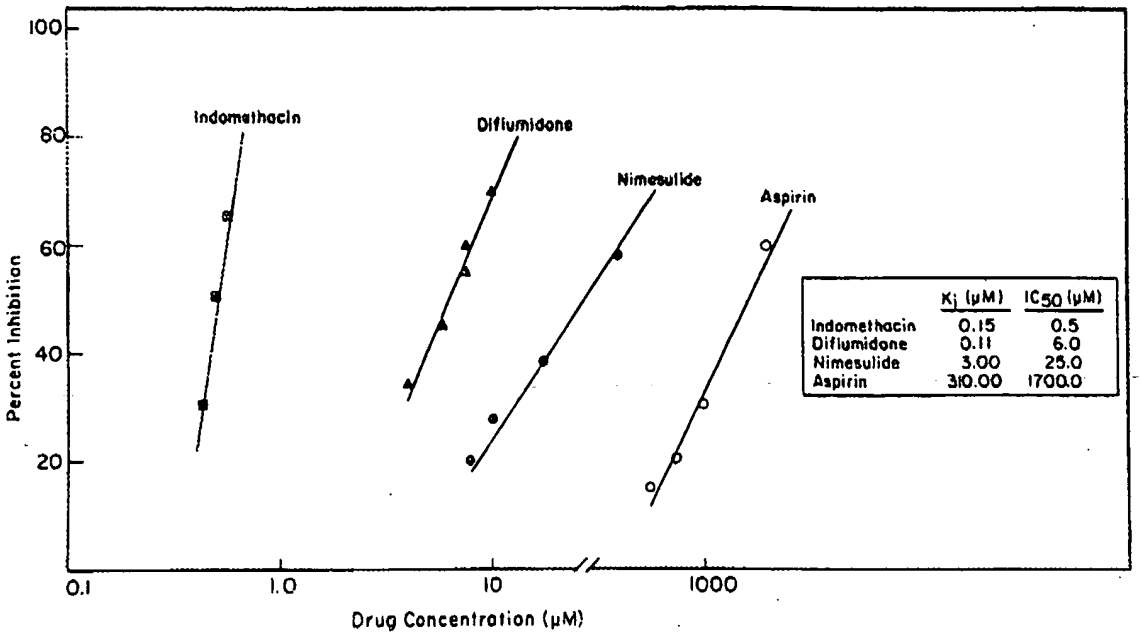

Fig. 11 Inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs.

Discussion

The authors speculate that metabolic activation of nimesulide occurs *in vivo*. The 4-nitro substituted molecule is uniquely potent among the anti-inflammatory sulfonanilides. Neither the 3-, 5- or 6-nitro isomers nor analogues with various substituents (e.g., methyl, chloro, amino, etc.) at the 4-position approach nimesulide in anti-inflammatory potency (unpublished data). The potency of nimesulide *in vivo* is much greater than would be predicted from its inhibition of prostaglandin synthetase *in vitro*. There is solid evidence that free radicals are involved in the enzymatic oxidation of arachidonic acid (15). Possible reactive metabolites of nimesulide include free radical species which could interact with free radical intermediates of arachidonic acid formed during its enzymatic oxidation. The uniqueness of the 4-nitro substituent of nimesulide suggests metabolic activation of the molecule to account for its anti-inflammatory activity *in vivo*. Oxidation of certain arenesulfonanilides yields an observable aminyl radical (Fig. 12). Based on structural considerations, the authors consider this type of oxidation to be unlikely for nimesulide. The one-electron reduc-

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Is the 4-NO_2 Group of Nimesulide Metabolically Activated?

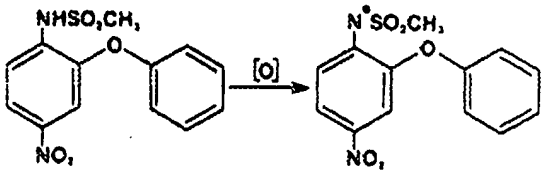
(1) 4-NO_2 ≫ 3-, 5-, or 6-NO_2 or 15 other substituents (e.g.; CH_3, Cl, NH_2...)

(2) In Vivo Potency ≫ In Vitro Potency

(3) Free Radicals Involved in Prostaglandin Synthesis

Possible Reactive Intermediates

(1) Oxidation



Unlikely

(2) Reduction

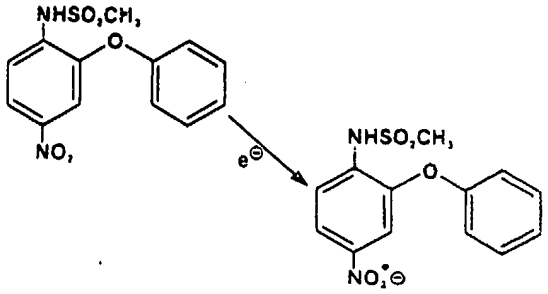


Fig. 12 Is the 4-NO_2 group of nimesulide metabolically activated?

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tion product shown in Fig. 12 resembles the proposed active metabolite involved in nitrofurantoin toxicity (16). The authors have no experimental evidence for this reduction product of nimesulide but suggest it as the possible reactive intermediate responsible for inhibition of synthesis of prostaglandins *in vivo*.

References

(1) Moore G.G.I. *Sulfonanilides with anti-inflammatory activity.* In: Scherrer R.A., Whitehouse M.W., eds. "Anti-Inflammatory Agents", Vol. I. Med. Chem. Ser. Monogr., Academic Press, New York, 1974, pp. 160-177.

(2) Moore G.G.I., Swingle K.F. *4-nitro-2-phenoxymethanesulfonanilide (R-805).* Abstr. 172nd Mtg. Amer. Chem. Soc., San Francisco, MEDI-63, 1976 (Abstr.).

(3) Swingle K.F., Hamilton R.R., Harrington J.K., Kvam D.C. *3-benzoyldifluoromethanesulfonanilide, sodium salt (diflumidone sodium, MBR 4164-9): a new anti-inflammatory agent.* Arch. Int. Pharmacodyn. Ther., **189**, 129, 1971.

(4) Swingle K.F., Moore G.G.I., Grant T.J. *4-nitro-2-phenoxymethanesulfonanilide (R-805): a chemically novel anti-inflammatory agent.* Arch. Int. Pharmacodyn. Ther., **222**, 132, 1976.

(5) Winter C.A., Risley E.A., Nuss G.W. *Carrageenan-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs.* Proc. Soc. Exp. Biol. Med., **111**, 544, 1962.

(6) Winder C.V., Wax J., Burr V., Been M., Rosiere C.E. *A study of pharmacological influences on ultraviolet erythema in guinea pigs.* Arch. Int. Pharmacodyn. Ther., **118**, 261, 1958.

(7) Swingle K.F. *Evaluation for anti-inflammatory activity.* In: Scherrer R.A., Whitehouse M.W., eds. "Anti-Inflammatory agents". Vol. II. Med. Chem. Ser. Monogr., Academic Press, New York, 1974, pp. 33-122.

(8) Swingle K.F., Grant T.J., Kvam D.C. *Quantal responses in the Randall-Selitto assay.* Proc. Soc. Exp. Biol. Med., **137**, 536, 1971.

(9) Data on file, Riker Labs., Inc., 3M Company, St. Paul, MN, USA.

(10) Randall L.O., Selitto J.J. *A method for measurement of analgesic activity on inflamed tissue.* Arch. Int. Pharmacodyn. Ther., **118**, 409, 1957.

(11) Chang S.F., Miller A.M., Ober R.E., Swingle K.F. *Metabolism of R-805, a new non-carboxylic acid, non-steroidal anti-inflammatory agent in rats.* Fed. Proc., **35** (3), 774, 1976 (Abstr.).

(12) Chang S.F., Miller A.M., Ober R.E. *Comparative absorption of R-805 formulations in man.* Amer. Pharmac. Assn. Acad. Pharmac. Sci., 19th Natl. Mtg., Atlanta, 1975, p. 132 (Abstr.).

(13) Rainsford K.D. *The comparative gastric ulcerogenic activities of non-steroidal anti-inflammatory drugs.* Agents Actions, **7**, 573, 1977.

(14) Vigdahl R.L., Tukey R.H. *Mechanism of action of novel anti-inflammatory drugs diflumidone and R-805.* Biochem. Pharmacol., **26**, 307, 1977.

(15) Swingle K.F., Bell R.L., Moore G.G.I. *Anti-inflammatory activity of antioxidants.* In: Rainsford K.D., ed. "Anti-rheumatic and anti-inflammatory drugs". CRC Press, Boca Raton, 1984 (in press).

(16) Mason R.P., Holtzman J.L. *The mechanism of microsomal and mitochondrial nitroreductase. Electron spin resonance evidence for nitroaromatic free radical intermediates.* Biochemistry, **14**, 1626, 1975.

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NIMESULIDE: A SELECTIVE CYCLOOXYGENASE 2 INHIBITOR ANTIINFLAMMATORY DRUG

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CONTENTS

Summary

Nimesulide is a sulfonanilide nonsteroidal antiinflammatory drug (NSAID) whose antiinflammatory, analgesic and antipyretic activities have been demonstrated in several widely used animal experimental models. The drug has shown potent antiinflammatory, analgesic and antipyretic activities when given orally or rectally twice daily at doses of 200 mg/day, although it is a relatively weak inhibitor of physiological prostaglandin synthesis. It acts rather as an inhibitor of oxygen free radicals and hypochlorous acid production and release in neutrophils without affecting their function, and as a potent and specific inhibitor of cyclooxygenase 2, the inducible form of the enzyme present in inflammatory cells. By respecting the activity of cyclooxygenase 1, nimesulide has a much lower risk of gastroduodenal lesions in comparison with most NSAIDs, a fact that may produce a significant improvement in the treatment of inflammatory diseases. Cyclooxygenase 2 is most probably involved in inflammatory reactions, in which significant contributions from free oxidants and extracellular proteases are also involved. Nimesulide has a high affinity and selectivity for cyclooxygenase 2, but it also acts as phosphodiesterase type IV inhibitor and has antiprotease effects against neutrophil elastase, cartilage collagenase and stromelysin. It is, thus, a multi-action compound with innovative antiinflammatory properties. In fact, the antiinflammatory efficacy of nimesulide has been demonstrated in clinical trials with patients with a large number of inflammatory conditions, including osteoarticular, otorhinolaryngological, odontological and other painful inflammatory processes, and its analgesic and antipyretic efficacies have also been controlled in a broad range of clinical situations. Furthermore, double-blind, comparative trials have shown nimesulide to be at least as effective as established NSAIDs, but with a trend toward a better side effects profile.

Introduction

Inflammation is a very complex process in which the activity of many cell types and mediators are

involved. Normally, tissue injury or the presence of foreign materials initiates a cascade of events which involves the participation of a complex battery of enzymes, mediators, fluid extravasation, cell migration and tissue breakdown and repair mechanisms that eventually result in the signs of inflammation: redness, swelling, heat, pain and loss of function. Stimuli that cause inflammation may be highly variable, but the process is mediated by a large but limited number of mediators, including prostaglandins, leukotrienes, interleukins, oxygen free radicals and other oxidants (nitric oxide, chloramines, hypochlorous acid), which apart from directly inducing tissue damage, inactivate protease inhibitors such as α_1-antitrypsin, the specific inhibitor of neutrophil elastase, thereby favoring digestion of the connective tissue matrix. These substances are produced by inflammatory cells, which include polymorphonuclear leukocytes (neutrophils, eosinophils, basophils), endothelial cells, mast cells, macrophages/monocytes and lymphocytes. Other stimuli leading to tissue inflammation include histamine, immunological events, chemotactic factors, and many more. Figure 1. shows a summary of the main inflammatory stimuli.

Prostanoids, which include prostaglandins and thromboxanes, and leukotrienes, are lipid mediators generated from membrane phospholipids by the action of several enzymes, which include phospholipase A_2, cyclooxygenase, lipoxygenase and enzymes specific for the synthesis of individual prostanoids. Prostaglandins, the products of the cyclooxygenase pathway that transforms arachidonic acid into the whole family of these autacoids, are involved in all phases of the inflammatory process, fever and pain reactions (1), as well as in a large

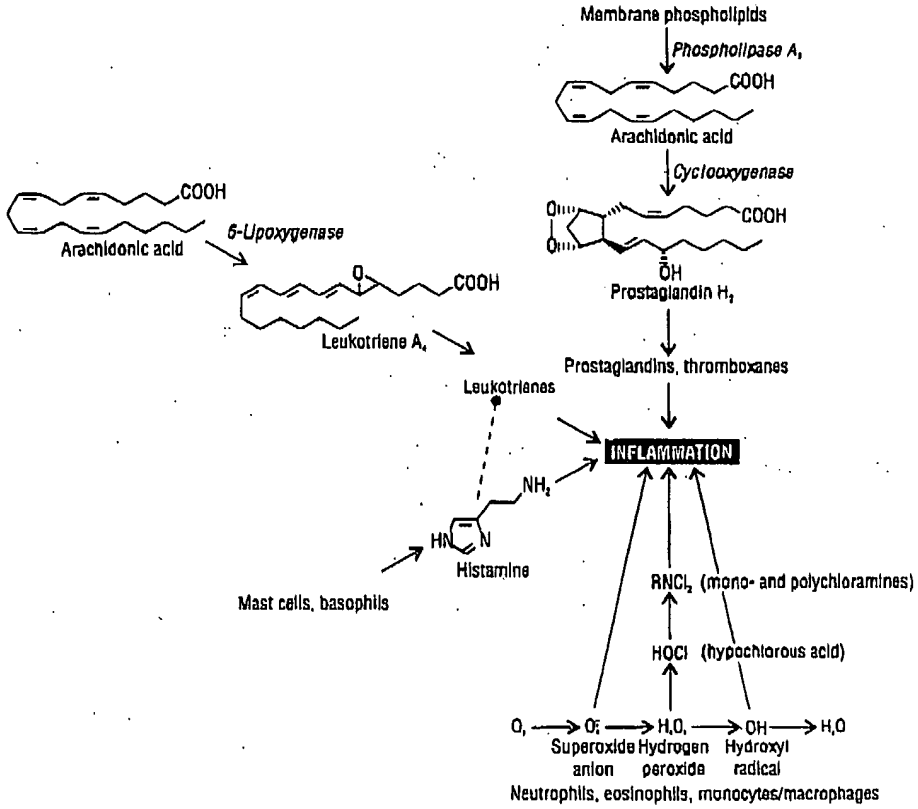


Fig. 1. Main stimuli leading to tissue inflammation. Inflammation may be the result of the action of prostaglandins and leukotrienes from polymorphonuclear cells, histamine released by mast cells and basophils, and oxygen free radicals produced by neutrophils and other inflammatory cells. Other secondary factors contributing to inflammation include proteolytic enzymes that mediate the digestion of the connective tissue matrix, immunoglobulins, complement, platelet-activating factor, neuropeptides, serotonin, interleukin and many others.

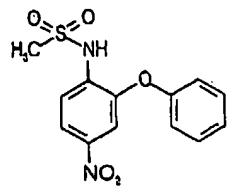
number of physiological functions, including intestinal motility, platelet aggregation, vascular tone, renal function, gastric secretion, gastric mucosal integrity, *etc.* (2).

Nonsteroidal antiinflammatory drugs (NSAIDs) are a nonhomogeneous family of pharmacologically active compounds that act mainly by blocking prostaglandin production; they are used in the treatment of acute and chronic inflammatory pain. These compounds are characterized by their ability to relieve pain, fever and inflammation associated with painful inflammatory disorders and other conditions (3), and include salicylates (acetylsalicylic acid, diflunisal, benorylate), anthranilic acid derivatives (mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid), phenylpropionic acid derivatives (fenoprofen, ibuprofen, naproxen, ketoprofen, flurbiprofen, fenbufen, tiaprofenic acid), indoles (indomethacin, ketorolac, sulindac, tolmetin, etodolac), oxicams (piroxicam, tenoxicam, meloxicam) and acetic acid derivatives (diclofenac, alclofenac). NSAIDs are thought to produce their therapeutic effects via the inhibition of cyclooxygenase, the rate-limiting enzyme that initiates the arachidonic acid cascade which leads to prostaglandin and thromboxane synthesis, thus preventing the production of proinflammatory prostaglandins, notably prostaglandin E_2 (PGE_2). However, the nonspecific inhibition of prostaglandin synthesis results in adverse events due to the lack of critical prostaglandins, which, in the stomach, is a cause of irritation and ulceration (4).

Nimesulide is an innovative sulfonanilide NSAID because it specifically inhibits not only the cyclooxygenase form found in inflammatory cells but also other substances leading to inflammation, such as free oxidants.

Mechanism of Action and Animal Pharmacology

Nimesulide is an innovative NSAID which is chemically different from other drugs in this class because of its functional acidic group in the sulfonanilide moiety (Fig. 2). Like all NSAIDs, nimesulide acts by inhibiting the synthesis of endogenous prostaglandins as a consequence of a blockade of the enzyme cyclooxygenase (prostaglandin-endoperoxide synthase [EC 1.14.99.1]), although it shows less potency than other NSAIDs in prostaglandin production tests *in vitro* (5-7). In contrast to indomethacin, nimesulide more potently inhibited PGE_2 and thromboxane A_2 production in inflammatory exudate than in the normal gastric mucosa of rats, and after subchronic administration for three days (up to 9 mg/kg p.o.), which is about seven times the antiinflammatory dose in the carrageenan rat paw edema



N-(4-Nitro-2-phenoxyphenyl)methanesulfonanilide

Fig. 2. Molecular structure and chemical name of nimesulide.

test, it did not modify urinary PGE_2 concentrations (8).

Nimesulide has exhibited potent antiinflammatory and analgesic activities in a number of experimental models of inflammation, including carrageenan-induced paw edema, Freund's complete adjuvant-induced arthritis and Randall-Selitto test in rats, UV-induced skin erythema in guinea pigs and phenylquinone-induced writhing in mice (9), and has been shown to be four times more potent than indomethacin in conventional antiinflammatory assays in rodents. In rats and guinea pigs it has an extremely favorable therapeutic ratio, with minimal acute gastrointestinal toxicity (5). However, the apparent *in vitro* activity of nimesulide on prostaglandin synthesis does not agree with its potent antiinflammatory activity in animal experimental models. Possible explanations for this may be a different mechanism of action, such as the formation and scavenging of free oxidants, which has been the object of many investigations, or the drug's selectivity for cyclooxygenase 2, the inducible form of the enzyme present in inflammatory cells.

Nimesulide and cyclooxygenase: selectivity for cyclooxygenase 2

The preliminary findings on the activity of nimesulide on prostaglandin formation did not directly reflect the weak inhibitory activity of nimesulide on cyclooxygenase, which is in contrast to the potent activity of most NSAIDs on this enzyme. Cyclooxygenase is a bifunctional, intracellular, membrane-bound heme-protein that catalyzes the bisoxygenation of arachidonic acid to prostaglandin G_2 and its subsequent reduction to prostaglandin H_2, thus initiating the prostanoid pathway of the arachidonic acid cascade (10). Subsequent transformations of prostaglandin H_2 give many prostaglandin and thromboxane types, including potent mediators of inflammation, as well as prostaglandins necessary for the correct functioning of many systems and organs, such as gastric mucosa protection, renal function, vascular homeostasis (prostaglandin I_2 or prostacyclin), smooth muscle contraction, parturition or platelet aggregation.

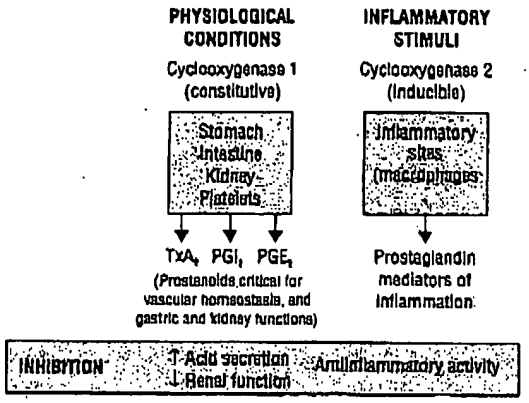


Fig. 3. Pathways of constitutive and inducible cyclooxygenases and consequences of their inhibition.

The discovery of two forms of the enzyme: the constitutive cyclooxygenase 1 (COX-1) and the inducible cyclooxygenase 2 (COX-2), which is induced by a variety of factors such as bacterial endotoxin (lipopolysaccharide), interleukin-1, phorbol esters and other mitogens, and is almost only found in stimulated inflammatory cells (Fig. 3) (11-17), gave a possible explanation for the weak effect of nimesulide found in previous assays. In fact, the drug was found to selectively inhibit COX-2 (IC_{50} = 10 nM), with a selectivity ratio *versus* COX-1 of >1000 (16, 18-21), which means that it is the most selective COX-2 inhibitor currently available. Furthermore, the inhibitory activity of nimesulide on COX-2 was found to be time-dependent (20).

As is apparent from Figure 4, combined data from several determinations of inhibitory potency against COX-1 and COX-2 in cells tests and purified enzyme (11, 17-26) shows that only four compounds, nimesulide, fluphenazine, niflumic acid and mefenamic acid, are selective for COX-2, with potency ratios greater than 10, nimesulide being the most selective among those currently available, with reported values as high as >1000 in some assays, according to Vane and Botting (25) (Table I). Most

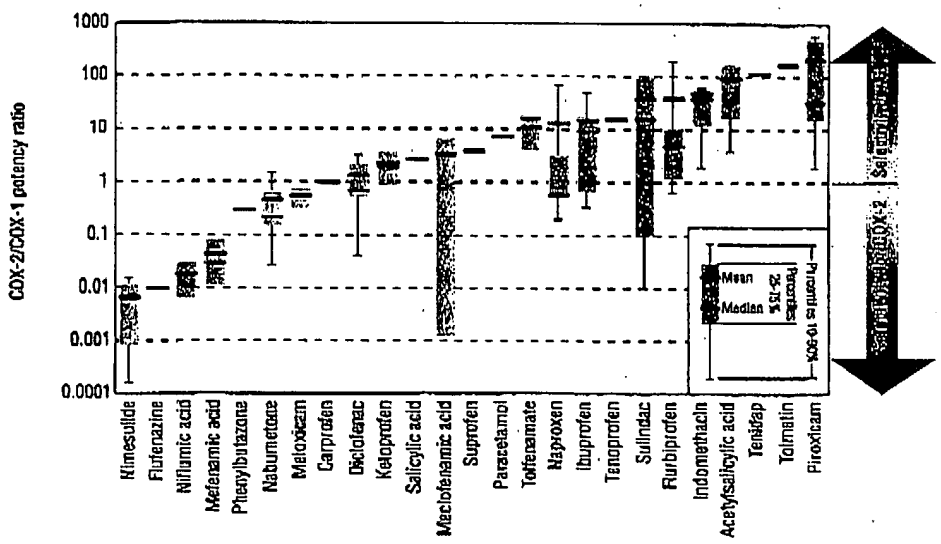


Fig. 4. Relative potency against cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) of several NSAIDs currently available. Data for nimesulide is biased, as reported values against cyclooxygenase 1 range from inactive (value not considered) to 0.01, with a median (depicted) of 0.007. (Data from refs. 11, 17-26.)

Table I: Comparative activities of nimesulide and representative nonsteroidal antiinflammatory drugs against cyclooxygenases type 1 and 2. Data correspond to potency ratios (IC_{50}) against cyclooxygenase 2/cyclooxygenase 1 in intact cell systems. (From Vane and Botting [25].)

Drug	Cyclooxygenase 2/ cyclooxygenase 1 ratio
Piroxicam	250
Tolmetin	175
Acetylsalicylic acid	166
Sulindac	100
Indomethacin	60
Tolfenamic acid	16.7
Ibuprofen	15
Paracetamol	7.4
Sodium salicylate	2.8
Flurbiprofen	1.3
Carprofen	1
Meloxicam	0.8
Diclofenac	0.7
Naproxen	0.6
Nimesulide	0.1

currently used NSAIDs, however, are COX-1 selective with potency ratios up to 100 (indomethacin, acetylsalicylic acid, tolmetin, piroxicam).

As COX-1 is responsible for the production of prostaglandins crucial for the normal hemostatic, gastric and renal function, whereas COX-2 is essentially present in inflammatory cells, the selectivity of action of nimesulide on COX-2 makes this drug largely devoid of most of the troublesome toxic effects of NSAIDs, especially on gastric prostaglandin synthesis and endothelial prostacyclin synthesis (risk of bleeding).

Interestingly, nitric oxide synthase, which regulates the production of nitric oxide, another potent inflammatory, vasodilator, platelet antiaggregatory mediator, has also been found to possess constitutive and inducible isoforms, and important interactions have been noted between the inducible form of nitric oxide synthase and COX-2. Both enzymes are highly sensitive to induction by endotoxins (lipopolysaccharide) and phorbol esters, and *in vitro* experiments have shown that many of the inducers of the COX-2 gene are also inducers of inducible nitric oxide synthase. Moreover, nitric oxide and prostaglandins, the respective products of nitric oxide synthase and COX-2, have been shown to cross-modulate the activity of their producing enzymes in a number of experimental models (17, 22).

Nimesulide and oxidants: oxygen free radicals and chloramines

The initial pharmacological studies showed that nimesulide, in addition to inhibiting prostaglandin synthesis, inhibits the production of oxygen free radicals as well (27). The drug also inhibits the generation of long-lived monochloramines and hypochlorous acid in neutrophils incubated with phagocytosible opsonized zymosan particles by means of scavenging and myeloperoxidase antagonism activities. As these chlorinated oxidants induce direct cell damage, but act as inactivators of protease inhibitors as well, the inhibition brought about by nimesulide results in a potent antiinflammatory effect (28-31). These activities of nimesulide are highly relevant, given that free radicals produced by neutrophils have been linked to the pathophysiology of many inflammatory diseases (32). Moreover, nimesulide, by scavenging the hypochlorous acid released by neutrophils through the action of myeloperoxidase, prevents the oxidative inactivation of α_1-proteinase inhibitor, further helping control the inflammation (33, 34). In another activity related to the action of free radicals, nimesulide was shown to inhibit the photohemolysis induced *in vitro* by tiaprofenic acid in red blood cells (35).

Other tests in neutrophils and monocytes from healthy volunteers treated with nimesulide showed that the drug inhibited *ex vivo* production of superoxide anion (O_2^-) when the cells were stimulated with the chemotactic formylated tripeptide *N*-formylmethionyl-leucyl-phenylalanine (fMLP), the calcium ionophore calcimycin (A-23187), the phorbol ester activator of protein kinases 12-*O*-tetradecanoylphorbol-13-acetate (TPA), which mediates the activation of neutrophils and macrophages, or opsonized zymosan particles (36-39).

The effect of nimesulide on O_2^- production may be related to its inhibitory activity on polymorphonuclear leukocyte cytosolic phosphodiesterase type IV (cAMP-specific), thus increasing cytosolic cAMP and, as a consequence, protein kinase A activity, which prompts the phosphorylation of a number of substrates and inhibits the assembly of NADPH-oxidase in the plasma membrane. Protein kinase A also interferes with chemotaxis; thus, nimesulide also inhibits stimulated chemotaxis. In fact, H-89[1], a specific protein kinase A inhibitor, was capable of counteracting the effect of nimesulide on fMLP- and TPA-induced O_2^- production and stimulated chemotaxis (38). Through the inhibition of phosphodiesterase type IV, nimesulide also reduces the activity of phospholipase A_2 as a result of the increased level of cAMP. By inhibiting phospholipase A_2, which is mainly responsible for arachidonic acid release from membrane phospholipids, nimesulide has a further inhibitory effect on the synthesis of prostaglandins,

[1] *N* - [2 - (2 - Bromocinnamylamino)ethyl]isoquinoline-5-sulfonamide.

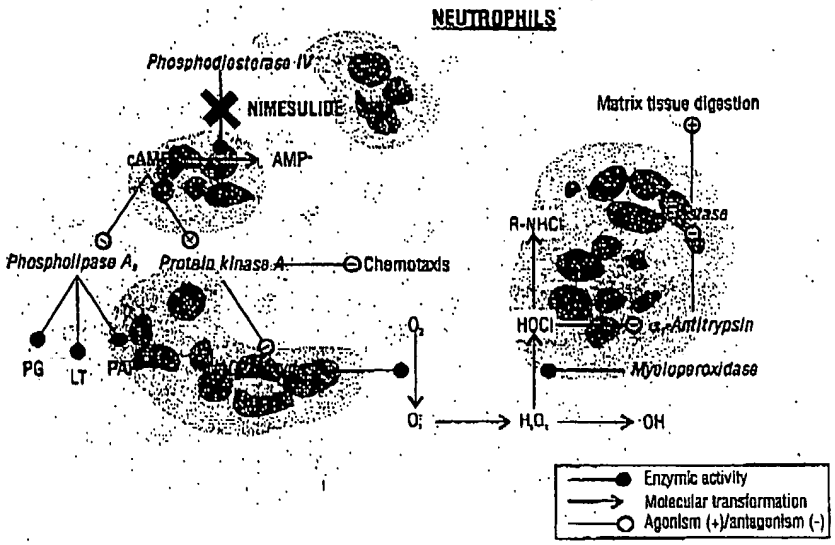


Fig. 5. Proposed mechanism of action of nimesulide on oxygen free radical formation and neutrophilic inflammation. Nimesulide has been shown to inhibit phosphodiesterase type IV, resulting in an accumulation of cAMP in polymorphonuclear leukocytes, inflammatory cells that contain most of the phosphodiesterase type IV isozyme. As a result of cAMP accumulation, protein kinase A is stimulated, which results in an inhibition of chemotaxis and NADPH oxidase activity, thus inhibiting the formation of O_2^-. The latter is dismutated to hydrogen peroxide (H_2O_2), which, by the action of myeloperoxidase, is transformed into hypochlorous acid (HOCl) which, in turn, is transformed into chloramines (R-NHCl) and inactivated α_1-antitrypsin, the enzyme that inhibits elastase and thus prevents the digestion of the intercellular connective matrix. Therefore, nimesulide, a potent antiinflammatory drug, adds to a potent cyclooxygenase 2 inhibition, a potent inhibitory activity on phosphodiesterase type IV (IC_{50} = 39 μM) that results in an inhibition of the formation of injurious free oxidants (O_2^-, H_2O_2, HOCl, •OH, R-NHCl [marked by white boxes in the drawing]), a prevention of chemotaxis and a prevention of the inactivation of α_1-antitrypsin, thus protecting the tissue matrix from digestion. On the other hand, as cAMP has an inhibitory effect on phospholipase A_2, the enzyme that by hydrolyzing membrane phospholipids forms arachidonic acid as a source for the generation of prostaglandins (PG), leukotrienes (LT) and platelet-activating factor (PAF), the effect of nimesulide on phosphodiesterase type IV further interferes with the production of these inflammatory mediators (40, 41, 166).

leukotrienes and platelet-activating factor, which complement the direct inhibitory activity on COX-2 (40).

At the same time, the interference with O_2^- formation brought about by nimesulide reduces the formation of chloramines, which also act as oxidative tissue damagers and inactivate α_1-antitrypsin, the physiological inactivator of elastase that prevents the digestion of the connective tissue matrix (41).

The general picture of nimesulide's action on phosphodiesterase type IV, oxygen free radicals and chloramines is illustrated in Figure 5.

The antioxidant activity of nimesulide, which was greater than that of its metabolites, was comparable to that of other potent antioxidant antiinflammatory agents, such as tenoxicam (42). The drug also inhibited hydrolytic enzyme release from neutrophils when incubated with calcimycin or fMLP, but not when the stimulating agent was TPA, and its activity was reversed by theophylline, a specific adenosine receptor antagonist, suggesting a role played by an adenosine-mediated mechanism (37). Nevertheless, as in previous tests, control of the neutrophil oxidative potential with nimesulide does not impair the cell's ability to handle microorganisms, and no increase in the incidence of infections has been observed during nimesulide treatment (43).

The inhibition of lipid peroxidation brought about by nimesulide was confirmed in rats with acute ethanol intoxication, in which the drug inhibited the hepatic increase in triacylglycerol and thiobarbituric acid reactive substance, with no changes in ethanol levels (44). Detailed analyses have shown that nimesulide inhibits neutrophil migration primarily by limiting cell anchorage to the tumor necrosis factor α-activated endothelium (45).

Nimesulide and extracellular proteases: role in articular and airway inflammation

Many osteoarthritic diseases are essentially the result of progressive erosions of the articular carti-

lage by three independent but closely related processes: i) enzymatic degradation; ii) reduced synthesis of matrix components; and iii) noxious effects of oxygen free radicals and other oxidants. As reported in the above sections, nimesulide inhibits the action of most free oxidants, but recent studies have suggested a role in blocking enzymes that degrade the cartilage matrix and in enhancing the synthesis of cartilage components as well.

Cartilage is attacked by cellular and molecular components of the inflammatory cascade: neutrophils can damage the cartilage matrix components and can inhibit the synthesis of proteoglycans. The neutrophil-mediated degradation of the cartilage matrix can be experimentally partially reverted by *N*-methoxysuccinyl-Ala-Ala-Pro-Val-chloromethylketone (MAAPV-CMK), a specific leukocyte elastase inhibitor, which suggests the involvement of enzyme activities, whereas some oxidants, particularly hypochlorous acid and hydrogen peroxide, also can mediate cartilage degradation and/or inhibit proteoglycan synthesis (46).

The two major components of the cartilage matrix are proteoglycans and collagen, and in patients with osteoarthritis a progressive depletion of proteoglycan, with modified structure (decreased content in hyaluronic acid) and an altered hydration and structure of type II collagen has been observed. Experimental studies using human articular cartilage from patients with osteoarthritis have shown that in *in vitro* conditions, nimesulide significantly inhibits the synthesis of stromelysin (proteoglycanase) and collagenase, two metalloproteinase enzymes degrading proteoglycans and collagen, respectively, whose activity is normally controlled by physiological α_1-proteinase inhibitors (tissue metalloproteinase inhibitors). The drug has, in consequence, a preventive role against cartilage matrix degradation (47). Moreover, as reported above, nimesulide by scavenging the hypochlorous acid released by neutrophils through the action of myeloperoxidase, prevents the oxidative inactivation of α_1-proteinase inhibitor (33, 34), further preventing cartilage degradation. In addition, by increasing cAMP levels as a result of the inhibition of phosphodiesterase type IV, nimesulide enhances the synthesis of proteoglycans (48). These phenomena may be an important advantage in the treatment of osteoarthritic diseases.

Similarly, nimesulide has been shown to inhibit the inactivation of α_1-antitrypsin through the inhibition of the production of free oxidants, thus preventing the overactivity of neutrophil elastase, an enzyme involved in many inflammatory disorders, for example of the airways. Neutrophil elastase is thought to be the most potent proteolytic enzyme, able to digest the major components of the connective tissue matrix, and its activity is physiologically regulated by α_1-antitrypsin, a compound primarily synthesized by hepatocytes and present in high concentrations in plasma and inflamed tissues. α_1-Antitrypsin can be inactivated through oxidation of a methionine residue mainly by attack by hypochlorous acid, which means that nimesulide has a role also in controlling the elastase/antielastase imbalance in inflammatory diseases of the airways (29, 30, 33, 34).

Other in vitro *activities of nimesulide*

Experimental studies in guinea pigs have shown that nimesulide possesses antihistaminic activity and inhibits immune-mediated release of histamine in a noncompetitive manner. The drug, at a dose of 1.6 μmol/kg i.v., inhibits both bronchoconstriction (69%) and thromboxane B_2 formation (93%) induced by histamine in anesthetized guinea pigs, whereas the release of histamine in isolated perfused lungs induced by an experimental anaphylactic reaction is lessened with an EC_{50} value of 3.06 μM. In isolated guinea pig trachea the activity of nimesulide was specific for the H_1 receptor type, with a potency nearly half that of mepyramine (pyrilamine maleate). Indomethacin failed to antagonize the bronchoconstrictor activity of histamine in guinea pig airways, and whereas nimesulide concentration-dependently reduced the anaphylactic release of histamine, indomethacin, in spite of inhibiting thromboxane B_2 formation, potentiated the immune release of histamine (49, 50).

Inhibition of the release of preformed histamine and *de novo* synthesized mediators of inflammation (leukotriene C_4 and prostaglandin D_2) by nimesulide was also demonstrated in incubated human basophils and mast cells stimulated with calcimycin, fMLP, TPA, the specific protein kinase C activator bryostatin and rabbit anti-human IgE antibody. On the contrary, acetylsalicylic acid, indomethacin and meclofenamic acid enhanced, rather than inhibited, IgE-mediated histamine release from human basophils (51, 52). Furthermore, in ovalbumin-sensitized guinea pigs challenged with antigen, inhaled nimesulide (0.1-1%) significantly delayed the respiratory burst and reduced blood histamine concentrations, as well as diminishing the experimental bronchoconstriction induced by intravenous acetaldehyde (53, 54).

The respiratory burst is inhibited by nimesulide independently of cytoplasm pH-regulating mechanisms, indicating that the drug does not act through Na^+/H^+-ATPase, which has been suggested to be one of the mechanisms of action of antiinflammatory drugs on NADPH oxidase and O_2^- release from

Table II: General pharmacology of nimesulide.

Pharmacological activity	Material/model	Results	Refs.
In vitro tests			
Inhibition of cyclooxygenase 1	Bovine seminal vesicle microsomes Bovine seminal vesicles	IC_{50} = 2.3 mM IC_{50} = 0.985 μM-inactive	7,11,19,20
Inhibition of cyclooxygenase 2	Sheep placenta	IC_{50} = 0.05-90.3 μM	1,19,20
Inhibition of PGE_2 production	Rabbit renal medulla microsomes Mouse fibroblasts/bradykinin-stimulated	IC_{50} = 0.02 μM IC_{50} = 1.36 pM	168
Inhibition of leukotriene production	Neutrophils/zymosan-induced —/fMLP-induced	IC_{50} = 10 μM IC_{50} = 50 μM	40
Inhibition of 5-HETE production[1]	Guinea pig peritoneal exudate cells/calcimycin-stimulated	IC_{50} > 0.3 μM	168
Inhibition of phosphodiesterase type IV[2]		IC_{50} = 39 μM	38
Inhibition of anaphylactic reaction	Sensitized isolated guinea pig lungs	IC_{50} = 3.06 μM	49
Inhibition of IgE-mediated TxB_2 formation	Sensitized isolated guinea pig lungs	IC_{50} = 3.35 μM	49
Scavenging of free radicals	Phosphatidylcholine liposomes	IC_{50} = 2.1-8.3 μM	165,169
Inhibition of oxidative reactions by •OH	Phosphatidylcholine liposomes	IC_{50} = 1.35 μM	169
Inhibition of lipid peroxidation	Rat liver microsomes	IC_{50} = 30 μM	42
Inhibition of proteinase release	Human leukocytes	IC_{30} = 0.03-0.06 μM	59
Inhibition of PAF synthesis	Neutrophils/zymosan-induced —/fMLP-induced	IC_{50} = 20 μM IC_{50} = 30 μM	40
In vivo and *ex vivo* tests[3]			
Inhibition of PGE_2 production	Rat gastric tissue (COX-1) Rat inflammatory exudate (COX-2)	ED_{50} = 15.7 mg/kg ED_{50} = 1.26 mg/kg	170
Inhibition of TxB_2 production	Rat gastric tissue (COX-1) Rat inflammatory exudate (COX-2)	ED_{50} = 17.9 mg/kg ED_{50} = 1.56 mg/kg	170
Inhibition of writhing	Mice/acetic acid-induced —/phenylquinone-induced —/acetylcholine-induced Rats/acetic acid-induced	ED_{50} = 40 mg/kg ED_{50} = 18 mg/kg ED_{50} = 10 mg/kg ED_{50} = 3-21 mg/kg	171,172
Inhibition of carrageenan-induced paw edema	Rats	ED_{50} = 2.0-2.8 mg/kg	9
Inhibition of paper disk granuloma formation	Rats	ED_{30} = 0.6 mg/kg	171
Inhibition of hind paw swelling	Rats with adjuvant arthritis	ED_{40} = 0.2-1.6 mg/kg/day	171-173
Inhibition of UV-induced erythema	Guinea pigs Rats	ED_{50} =1.4- 4.5 mg/kg ED_{50} = 2.3 mg/kg x 2	9,171
Analgesic activity	Rats/Randall-Selitto test —/yeast-induced hyperesthesia	ED_{50} = 3.5-5.2 mg/kg ED_{50} = 5.2 mg/kg	9,171
Hypothermic activity	Rats/yeast-induced fever	ED_{50} = 0.2-0.5 mg/kg	171,174
Inhibition of platelet aggregation	Guinea pig platelet-rich Plasma/ADP-induced —/arachidonic acid-induced —/collagen-induced	ED_{50} = 2.71 mg/kg ED_{50} = 1.65 mg/kg ED_{50} = 1.65 mg/kg	174
Inhibition of antigen-induced dyspnea	Ovalbumin-sensitized guinea pigs	ED_{175} = 1.6 mg/ml inhal	175
Inhibition of histamine production	Ovalbumin-sensitized guinea pigs	ED_{25} = 2.7 mg/ml inhal	175

[1]5-Hydroxyeicosatetraenoic acid. This test rules out an action of the drug on the 5-lipoxygenase arachidonic acid cascade leading to leukotriene synthesis. [2]Related to O_2^- formation and histamine release. [3]All values reported correspond to oral administration of the drug.

neutrophils (55). In contrast to acetylsalicylic acid or indomethacin, which can induce bronchoconstriction in patients with intolerance to acetylsalicylic acid or other NSAIDs or bronchial asthma, nimesulide generally does not lead to severe obstructive reactions in these kind of patients. This is a further confirmation of the very good safety profile of the drug also in populations "at risk" (56-58). This lack of obstructive reactions may be related to the inhibitory effect of nimesulide on IgE-related, histamine-mediated bronchoconstriction and on the weak inhibitory activity of leukotriene production.

Comparative experimental tests have shown that nimesulide inhibits the activation of rat peritoneal and bronchoalveolar leukocytes and human leukocytes stimulated with opsonized zymosan, and also inhibits the release of proteinase from human leukocytes, nimesulide being more potent than indomethacin and nedocromil sodium (59).

Table II shows the main pharmacological findings with nimesulide in *in vitro* and *in vivo* studies in animals.

Toxicity

Acute and chronic toxicity studies on nimesulide produced LD_{50} (acute studies) and noneffect doses (chronic studies) much higher than the oral antiinflammatory doses in mice, rats and dogs, according to data on file in Helsinn Healthcare, S.A. On the contrary, the results of reproductive toxicity assessments suggest that nimesulide should not be given to pregnant women due to the risk of teratogenicity demonstrated with high doses in rabbits. On the other hand, nimesulide was shown to be nonmutagenous in an Ames test and several other mutagenic tests (60).

The main toxicity of NSAIDs in clinical use is the risk of gastric ulcer, which has been the object of systemic experimental and clinical studies. In a comparison with indomethacin, nimesulide exhibited a UD_{50} value of >20 mg/kg p.o., whereas the corresponding value for the reference compound was 1.6 mg/kg p.o. This fact reveals the lower gastrotoxicity profile of nimesulide, which is the main toxicity concern of NSAIDs (8).

Clinical Evaluation

The greatest anticipated benefit of a selective COX-2 inhibitor will be a favorable side effect profile with no loss of antiinflammatory activity in comparison with standard NSAIDs, which is of the utmost importance for chronic treatments in elderly patients, those most frequently attained by rheumatic processes requiring long-term analgesic and antiinflammatory treatment. Nimesulide, the first COX-2 inhibitor to reach the market, has been tested in controlled clinical trials in patients with a very high spectrum of inflammatory, painful and/or hyperthermic conditions in adult, pediatric and elderly patients, including patients with osteoarticular (27, 61-73), otorhinolaryngological (74-79), odontological (80-88), respiratory (89, 90), vascular (91-93), male (94, 95) and female genitourinary (96-99) (dysmenorrhea [(100-104]) and other painful inflammatory processes as well as patients with fever of varying etiology (105-118 and pain from surgery and traumas (119-128) or chronic pain from other etiologies (129-131). Furthermore, although bacterial infectious diseases require adequate antibacterial agents, antiinflammatory drugs can be given for symptomatic relief of pain and inflammation. Nimesulide has also been used as adjuvant treatment in patients with bacterial infectious disease (132-142).

In all these clinical trials, nimesulide at the recommended oral dose of 100 mg b.i.d., has shown antiinflammatory, analgesic and antipyretic efficacy comparable or superior to usual reference NSAIDs (acetylsalicylic acid, metamizole [dipyrone], diclofenac, piroxicam, naproxen, etodolac, flurbiprofen, ketoprofen, mefenamic acid) and good or excellent tolerability, mild and transient adverse reactions being observed in <10% of patients.

The first postmarketing survey in the short-term treatment of osteoarthritis, involving a total of 22,938 patients, was published in 1991 (61). The drug was given as tablets or granules at doses of 100-400 mg/day for 1-3 weeks, and the treatment was effective in relieving spontaneous pain and stiffness with a low incidence of side effects (8%), mostly gastrointestinal discomfort.

The most favorable dose of the drug in terms of efficacy/safety has been calculated as 100 mg b.i.d. in a recent multicenter, double-blind, parallel clinical trial in 392 patients with osteoarthritis; doses of 50 and 100 mg b.i.d. were well tolerated, whereas doses of 200 mg b.i.d. led to a higher but nonsignificant incidence of side effects. On the other hand, significant analgesia was obtained within 1.5 hours with the dose levels of 100 and 200 mg b.i.d., thus the dose of 100 mg b.i.d. was determined as the most adequate (73).

The results of the comparative trials with nimesulide and reference NSAIDs in terms of clinical efficacy are summarized in Figure 6.

Nimesulide also proved to be effective in pediatric patients; the major results of most trials are illustrated by a trial in 6055 children with diverse inflammatory affections in which a highly statistically significant regression of signs and symptoms of pain and inflammation was seen, with good or excellent tolerability in 99.62% of the patients (143).

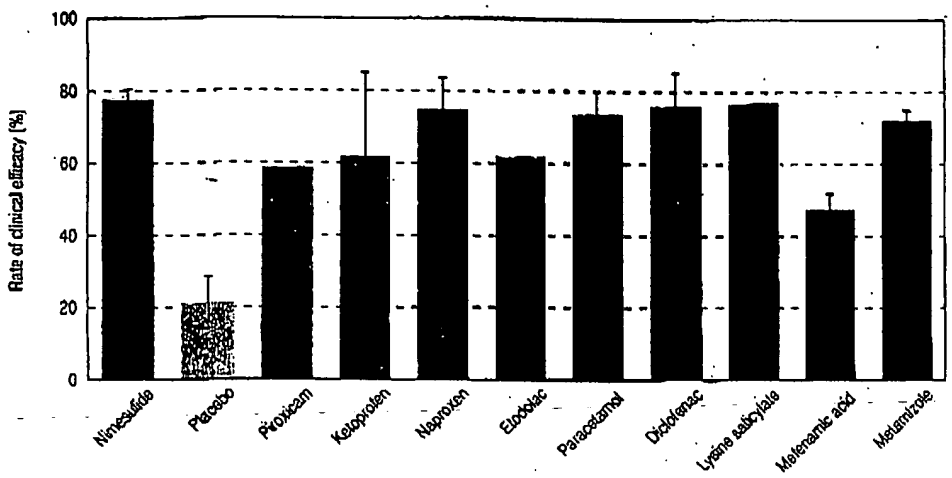


Fig. 6. Clinical efficacy of nimesulide (50-200 mg b.i.d.) and reference NSAIDs in the symptomatic treatment of painful inflammatory diseases. (Data correspond to the comparative trials presented in the text.)

Side Effects and Drug Interactions

Most clinical studies comparing nimesulide to other NSAIDs have documented similar or greater efficacy of the new compound as regards analgesic, antiinflammatory and hypothermic activities, with the advantage of its better tolerability in adult, pediatric and elderly patients (64, 74, 137, 144). A trial conducted in healthy volunteers with doses up to 600 mg/day p.o. for 7 days has shown no evidence of clinically significant alterations in hematological or biochemical assays or nephrotoxicity, while doses of 800 mg/day, twice the highest recommended dose, were associated with abdominal pain in 5/8 (62.5%) patients (145). Epidemiological data from 151 trials with nimesulide revealed an overall incidence of side effects of 349/4945 (7.1%) patients, with a rate of withdrawal due to toxicity of 52/4945 (1.1%). The majority of adverse reactions recorded affected the digestive system (72.1%), followed by the body as a whole (11.7%), the skin (6.9%) and the nervous system (6.0%). However, the incidence and nature of such adverse events were similar to those observed in the corresponding placebo groups of each clinical trial, demonstrating the good tolerability of nimesulide (146).

The long-term tolerability of the drug was assessed in a nonblinded fashion in a group of 134 patients with osteoarthritis treated with doses of 100 mg p.o. b.i.d. for 1 year. Good clinical tolerance was observed in 77% of patients, with poor tolerance in only 7%. The most frequently reported adverse events were gastrointestinal complaints (51% of total adverse reactions observed), followed by central nervous system (6.8%) and skin reactions (6.8%). In general, adverse reactions were mild and transient, severe reactions being observed in only 9/133 (6.8%) patients. The incidence of side effects decreased with increased treatment duration (Fig. 7) (147).

The main concern regarding the adverse reactions of all NSAIDs is the risk of gastric irritation resulting from the inhibition of endogenous prostaglandin production. NSAIDs are known to provoke or exacerbate gastroduodenal lesions and ulcers in four distinct ways: (i) causing acute mucosal injury, with intramucosal hemorrhage, that leads to diffuse erosion and ulceration; (ii) interfering with platelet function, with an increased risk of bleeding from preexisting lesions; (iii) provoking solitary ulcers in chronic administration of relatively high doses; and (iv) exacerbating ulcers and causing ulcer complications in patients with preexisting peptic ulcer disease (148). Other factors that may contribute to tissue lesions include free oxidants (O_2^-, hypochlorous acid) and extracellular proteases acting on the tissue matrix. NSAIDs, in general, do not enhance the production of such factors, but they do not prevent its pathological activation either.

NSAIDs are a nonhomogeneous drug family characterized by a potent inhibitory activity on cyclooxygenase, the enzyme that leads to the synthesis of proinflammatory prostanoids but also of prostaglandins critical for the correct gastric protection and renal function, among other important effects. As a consequence, treatment with NSAIDs relieves inflammation, but has deleterious effects on gastric mucosa (risk of peptic ulcer). In addition, these compounds have been associated with other significant side effects, which include nephrotic syndrome, acute interstitial nephritis, and electrolyte and water

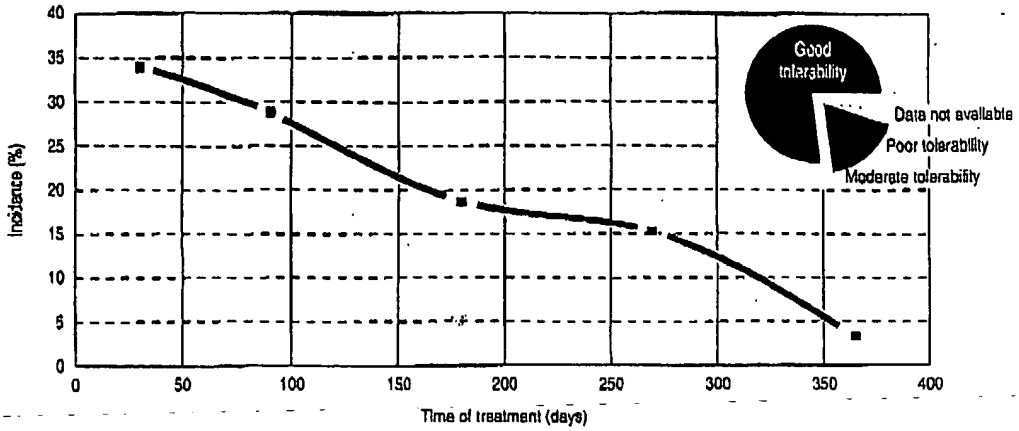


Fig. 7. Incidence of side effects during long-term treatment with nimesulide. The actual incidence of side effects through time and the global tolerability profile of the drug in long-term treatment (insert) are shown. (Data from ref. 147.)

disturbances, especially after chronic treatment of rheumatoid arthritis in the elderly (149).

However, nimesulide, by its low activity on COX-1 and a selectivity ratio of >1000 for COX-2, may have a better ulcerogenic profile in comparison with standard drugs of this class, which may depend on its not inhibiting significantly the cyclooxygenase subtype present in gastric cells and responsible for the synthesis of critical, physiological prostaglandins and thromboxanes required for vascular homeostasis and gastric and kidney functions. Furthermore, the drug also acts as a phosphodiesterase type IV inhibitor and free radical scavenger, and also protects the tissues from protease-mediating degradation. The sum of all these facts: selective inhibition of COX-2, inhibition of phosphodiesterase type IV, scavenging of free oxidants and prevention of the activity of collagenase and elastase means that nimesulide not only is active by different mechanisms as an antiinflammatory, but also has a protective role complementary to its antiinflammatory activity on gastric mucosa as well as in cartilages and the airways wall, for example.

In fact, in a comparative, single-blind trial in 32 patients with articular inflammatory diseases, in which the gastric toxicity of nimesulide (200 mg/day) and indomethacin (150 mg/day) was compared after 12-15 days of treatment by means of an endoscopic examination, both drugs were equipotent, but nimesulide was related to fewer gastric injurying effects (150). In this respect, nimesulide (100 and 200 mg b.i.d.) was compared to placebo in 30 dyspeptic patients, and gastric injuries were observed in one subject receiving each nimesulide dose and two

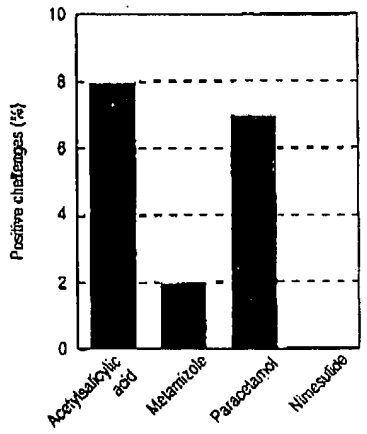


Fig. 8. Comparative positive challenges of nimesulide, other NSAIDs and paracotamol on endoscopically examined gastric mucosa. Data correspond to the results of oral challenges with various antiinflammatory drugs in patients with known intolerance to NSAIDs. (Data from ref. 152.)

patients in the control group, with an incidence of adverse effects comparable in all groups (151, 152).

A further comparison between nimesulide and diclofenac in patients with osteoarthritis examined by endoscopy revealed no statistically significant differences in the gastrotoxicity of both drugs (153), even if a slightly positive trend was seen in favor of nimesulide treatment.

Moreover, oral challenges with various NSAIDs and paracetamol in 112 patients with proven intolerance to NSAIDs revealed no positive challenges to nimesulide (Fig. 8), whereas further assessments

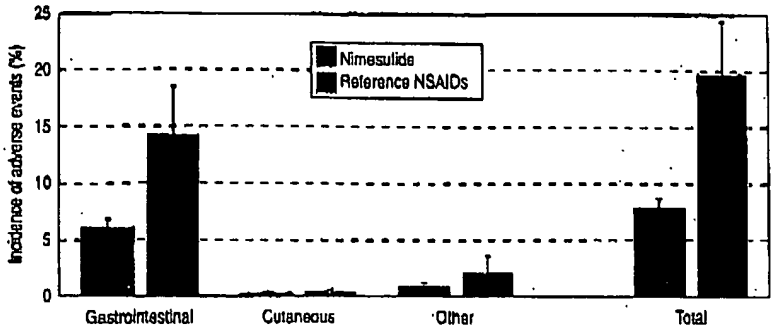


Fig. 9. Incidence of side effects in the clinical trials presented in the text with nimesulide and reference NSAIDs (64-67, 91, 96-98, 105-112, 134-139, 167).

with nimesulide in 284 and 429 patients with intolerance to NSAIDs (mainly acetylsalicylic acid) showed mild drug-induced positive reactions in only 14/284 (4.9%) and 11/429 (3.3%) of them (154, 155). These studies point out the usefulness of nimesulide in patients with hypersensitivity or intolerance to acetylsalicylic acid and other NSAIDs, who require treatment for concomitant inflammatory diseases.

On the other hand, nimesulide has been rarely associated with the troublesome cutaneous reactions induced frequently by other NSAIDs (urticaria/angioedema, fixed eruptions, exanthemas, erythema multiforme, Stevens-Johnson syndrome), especially the salicylates (acetylsalicylic acid), the pyrazolones (pheprazone, metamizole), the fenamates (mefenamic acid, meclofenamic acid) and the oxicams (piroxicam, tenoxicam) (156, 157). Nimesulide also has a better profile in comparison with other NSAIDs in terms of the risk of urticaria/angioedema, bronchial asthma or polymorphous erythema in atopic patients (158), although a fixed eruption in reaction to the drug has been identified in an Italian epidemiological analysis (159).

The overall comparative side effects profile of nimesulide and representative reference NSAIDs is summarized in Figure 9.

With respect to drug interactions, nimesulide has been shown to decrease the oral bioavailability of furosemide and to displace fenofibrate, salicylic acid and tolbutamide from plasma protein binding. No other interactions have been reported to date (160). Moreover, although some authors have reported an interaction between nimesulide and warfarin, with an increased risk of bleeding, a study in 10 patients treated concomitantly with 100 mg b.i.d. nimesulide and 5 mg/day warfarin did not show statistically significant differences in prothrombin time, partial thromboplastin time, fibrinogenemia or bleeding time. The findings suggested that short-term treatment with nimesulide does not increase the bleeding risk of warfarin (161). No interaction has been observed with short-term nimesulide (7 days) and digoxin (0.2 mg/day) in patients with heart failure (162).

Conclusions

Nimesulide is a multi-action antiinflammatory compound. It inhibits prostaglandin production by selectively inhibiting the cyclooxygenase pathway leading to the production of proinflammatory prostaglandins. It also inhibits the production of oxidants (oxygen free radicals, long-lived monochloramines, hypochlorous acid) from activated neutrophils and other inflammatory cells, the release of histamine from mast cells and basophils, and the production of platelet activating factor by neutrophils and basophils (163). The drug also has a scavenging effect on the oxidants released from polymorphonuclear cells and recent studies have shown it to block the activity of stromelysin and other matrix metalloproteinases in human articular chondrocytes, an enzyme system which is involved in the pathophysiology of osteoarticular disorders (47, 48). Furthermore, as leukotriene production in polymorphonuclear cells can also be modulated by histamine, nimesulide also has an inhibitory effect on leukotriene production.

The clinical trials briefly reviewed in this report have clearly demonstrated the good efficacy and the tolerability of nimesulide in the treatment of the classical inflammatory diseases that are the main indications of NSAIDs, namely inflammatory osteoarticular diseases. The drug has also been very successful as an analgesic in dental conditions and surgery, and as regards inflammatory processes of the upper respiratory tract, nimesulide has been documented to be highly effective in relieving symptoms of rhinitis, sinusitis, rhinopharyngitis, tubaritis and secretory otitis media, with the concomitant antibiotic treatment of underlying infectious diseases (164). In this

broad spectrum of pathologies nimesulide has been at least as effective as representative reference anti-inflammatory drugs, such as acetylsalicylic acid, paracetamol, naproxen, diclofenac, *etc.*, with the advantage of a tendency towards a lower incidence of side effects, especially with respect to gastrointestinal tolerance.

One of the main advantages of nimesulide is its tolerability profile. NSAIDs are known to have injurious effects on mucosal protection and repair, and chronic treatment may lead to peptic ulcers. However, the demonstration that proinflammatory prostaglandins are synthesized by an inducible form of cyclooxygenase (COX-2) has opened a new era of research in the treatment of inflammatory diseases, as compounds that selectively inhibit this isoform would be expected to be antiinflammatory without the gastrointestinal and renal toxic effects of standard NSAIDs, which are believed to be due to the inhibition of the constitutive enzyme COX-1 (17, 22, 24, 149). Nimesulide, which was a drug available before the discovery of COX-1 and COX-2 isoforms and whose exact mechanism of action was highly unknown since no marked inhibition of physiological prostaglandin synthesis was found, has been recently shown to selectively inhibit COX-2, the inducible form of the enzyme present only in sites of inflammation, respecting the constitutive isoform, COX-1, which contributes to the synthesis of prostanoids crucial for mucosal defenses. As a consequence, nimesulide has a very low ulcerogenic risk in comparison with classical NSAIDs, which may reduce the risk of mucosal injuries during treatment of inflammatory diseases. Furthermore, there is increasing evidence that direct injury to both mucosae and endothelia is mediated by free-radical species, exacerbated by reduced blood flow and by the release of inflammatory mediators that enhance vascular leakage and hemorrhage (148). Nimesulide, which also inhibits the production and/or scavenges released free radicals, may further contribute to mucosal defenses, while augmenting the antiinflammatory potency. These pharmacological data have also been confirmed in clinical studies both in healthy volunteers and in patients with intolerance to NSAIDs, in particular in endoscopic assessments of potential gastric damage upon administration of nimesulide or comparative reference NSAIDs (Fig. 8).

Although several authors expressed fears that a COX-2 selective inhibitor might be less potent as an antiinflammatory and analgesic than classical NSAIDs, due partly to the feeling that even if it is evident that COX-2 is mainly an inducible enzyme involved in the inflammatory and mitogenic processes and COX-1 is a constitutive enzyme involved in normal functioning of several organs, it is possible that the opposite is partly true as well (165). However, the results obtained with nimesulide, the first COX-2 selective inhibitor to be extensively used, demonstrate that despite its poor activity on COX-1, it is at least as effective as other NSAIDs but shows a better tolerability, especially regarding gastrointestinal toxicity.

References

1. Sala, A., Folco, G. *Actual role of prostaglandins in inflammation.* Drug Invest 1991, 3 (Suppl. 2): 4-9.
2. Davier, P., Bailey, P.J., Goldenberg, M., Ford-Hutchinson, A.W. *The role of arachidonic acid oxygenation products in pain and inflammation.* Annu Rev Immunol 1984, 2: 335-357.
3. Cullen, E. *Novel anti-inflammatory agents.* J Pharm Sci 1984, 73: 579-589.
4. Allison, M.C., Howatson, A.G., Torrance, C.J., Lee, F.D., Russell, R.I. *Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs.* New Engl J Med 1992, 327: 749-754.
5. Swingle, K.F., Moore, G.G.I. *Preclinical pharmacological studies with nimesulide.* Drugs Exp Clin Res 1984, 10: 587-597.
6. Magni, E. *Nimesulide. An overview.* Drug Invest 1991, 3 (Suppl. 2): 1-3.
7. Magni, E. *The effect of nimesulide on prostanoid formation.* Drugs 1993, 46 (Suppl. 1): 10-14.
8. Ceserani, R., Casciarri, I., Cavalletti, E., Cazzulani, P. *Action of nimesulide on rat gastric prostaglandins and renal function.* Drug Invest 1991, 3 (Suppl. 2): 14-21.
9. Velo, G.P. *The anti-inflammatory, analgesic and antipyretic activity of nimesulide in experimental methods.* Drug Invest 1991, 3 (Suppl. 2): 10-13.
10. Garavito, R.M., Picot, D., Loll, P.J. *The X-ray structures of complexes of cyclooxygenase-1 and inhibitors.* Med Chem Res 1995, 5: 375-383.
11. Aslanian, R., Carruthers, N.I., Kaminski, J.J. *Cyclooxygenase-2: A novel target for therapeutic intervention.* Expert Opin Invest Drugs 1994, 3: 1323-1325.
12. Xie, W., Chipman, J.G., Robertson, D.L., Erikson, R.L., Simonsons, D.L. *Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing.* Proc Natl Acad Sci USA 1991, 88: 2692-2696.
13. O'Banion, M.K., Sadowski, H.B., Winn, V., Young, D.A. *A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase related protein.* J Biol Chem 1991, 266: 23261-23267.

14. Kujubu, D.A., Herschmann, H.R. *Dexamethasone inhibits mitogen induction of the TIS10 prostaglandin synthase/cyclooxygenase gene.* J Biol Chem 1992, 267: 7991-7994.
15. Sirois, J., Richards, J.S. *Purification and characterization of a novel, distinct isoform of prostaglandin endoperoxide synthase induced by human chorionic gonadotropin in granulosa cells of rat preovulatory follicles.* J Biol Chem 1992, 267: 6382-6388.
16. Barnett, J., Chow, J., Ives, D. et al. *Purification, characterization and selective inhibition of human prostaglandin G/H synthase 1 and 2 expressed in the baculovirus system.* Biochim Biophys Acta 1994, 1209: 130-139.
17. Vane, J.R., Botting, R.M. *New insights into the mode of action of anti-inflammatory drugs.* Inflamm Res 1995, 44: 1-10.
18. Taniguchi, Y., Ikesue, A., Yopkoyama, K. et al. *Selective inhibition by nimesulide, a novel nonsteroidal anti-inflammatory drug, with prostaglandin endoperoxide synthase-2 activity in-vitro.* Pharm Sci 1995, 1: 173-175.
19. Tavares, I.A., Bishai, P.M., Bennett, A. *Activity of nimesulide on constitutive and inducible cyclooxygenases.* Arzneim Forsch/Drug Res 1995, 45: 1-3.
20. Vago, T., Bevilacqua, M., Norbiato, G. *Effect of nimesulide action time dependence on selectivity towards prostaglandin G/H synthase/cyclooxygenase activity.* Arzneim Forsch/Drug Res 1995, 45: 4-6.
21. Grossman, C.J., Wiseman, J., Lucas, F.S., Trevethick, M.A., Birch, P.J. *Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and COX 2 inhibitors.* Inflamm Res 1995, 44: 253-257.
22. Battistini, B., Botting, R., Bakhle, Y.S. *COX-1 and COX-2: Toward the development of more selective NSAIDs.* Drug News Perspect 1994, 7: 501-512.
23. Vojnovic, I., Amirmansour, C., Warner, T.D., Vane, J.R. *Nimesulide: Selectivity for COX-2 over COX-1.* Improved Non-Steroid Anti-Inflammatory Drugs: COX-2 Enzyme Inhibitors, London 1995.
24. Hayllar, J., Bjarnason, I. *NSAIDs,COX-2 inhibitors, and the gut.* Lancet 1995, 346: 521-522.
25. Vane, J.R., Botting, R.M. *Overview: Mechanisms of action of anti-inflammatory drugs.* In: Vane, J.R., Botting, J., Botting, R. (Eds.). Improved Non-Steroid Anti-Inflammatory Drugs. COX-2 Enzyme Inhibitors. Kluwer Academic Publishers/William Harvey Press 1996, 1-27.
26. Tavares, I.A., Bishai, P.M., Bennett, A. *Nimesulide selectively inhibits cyclo-oxygenase-2 activity in vitro.* Unpublished 1995.
27. Magaro, M., Altomonte, L., Zoli, A., Mirone, L., Corvino, G., Berchicci, M. *Nimesulide in the treatment of osteoarthritis and non-articular rheumatism.* Minerva Med 1989, 80: 1015-1018.
28. Dallegri, F., Dapino, P., Ottonello, L., Guidi, G. *Suppression of neutrophil chloramine production by nimesulide. A possible contribution to the anti-inflammatory activity of the drug.* Drug Invest 1991, 3 (Suppl. 2): 75-78.
29. Ottonello, L., Dapino, P., Pastorino, G. et al. *Nimesulide as a downregulator of the activity of the neutrophil myeloperoxidase pathway: Focus on the histoprotective potential of the drug during inflammatory processes.* Drugs 1993, 46 (Suppl. 1): 29-33.
30. Ottonello, L., Dapino, P., Dallegri, F. *Inactivation of α-1 protelnase inhibitor by neutrophil metalloproteinases: Crucial role of the myeloperoxidase system and effects of the anti-inflammatory drug nimesulide.* Respiration 1993, 60: 32-37.
31. Ottonello, L., Dapino, P., Scirocco, M.C., Balbi, A., Bevilacqua, M., Dallegri, F. *Sulphonamides as anti-inflammatory agents: Old drugs for new therapeutic strategies in neutrophilic inflammation?* Clin Sci 1995, 88: 331-336.
32. Sacchetti, C., Dallegri, F., Patrone, F. *Neutrophils as effectors of host defense and host damage. Physiopathology and perspectives of pharmacological manipulation.* Int J Immunopathol Pharmacol 1989, 2: 67-73.
33. Dallegri, F., Ottonello, L., Dapino, P., Sacchetti, C. *Effect of nonsteroidal antiinflammatory drugs on the neutrophil promoted inactivation of α-1-proteinase inhibitor.* J Rheumatol 1992, 19: 419-423.
34. Dallegri, F., Ottonello, L., Dapino, P., Bevilacqua, M. *The anti-inflammatory drug nimesulide rescues α-1-proteinase inhibitor from oxidative inactivation by phagocytosing neutrophils.* Respiration 1992, 59: 1-4.
35. Fontes Ribeiro, C.A., Figueiredo, A., Tavares, P., Poiares Baptista, A., Teixeira, F. *Tiaprofenic acid-induced photohemolysis in vitro is inhibited by nimesulide.* Drug Metab Drug Interact 1992, 10: 293-305.
36. Ottonello, L., Dapino, P., Pastorino, G., Dallegri, F. *Inhibition of the neutrophil oxidative response induced by the oral administration of nimesulide in normal volunteers.* J Clin Lab Immunol 1992, 37: 91-96.

37. Capecchi, P.L., Ceccatelli, L., Beermann, U., Laghi Pasini, F., Di Perri, T. *Inhibition of neutrophil function in vitro by nimesulide. Preliminary evidence of an adenosine-mediated mechanism.* Arzneim Forsch/Drug Res 1993, 43: 992-996.
38. Bevilacqua, M., Vago, T., Baldi, G., Renesto, E., Dallegri, F., Norbiato, G. *Nimesulide decreases superoxide production by inhibiting phosphodiesterase type IV.* Eur J Pharmacol 1994, 268: 415-423.
39. De Mello, S.B., Laurindo, I.M., Cossermelli, W. *Action of the 4-nitro-2-phenoxymethanesulphonanilide (nimesulide) on neutrophil chemotaxis and superoxide production.* Rev Paul Med 1994, 112: 489-494.
40. Tool, A.T.J., Verhoeven, A.J. *Inhibition of the production of platelet activating factor and of leukotriene B_4 in activated neutrophils by nimesulide due to an elevation of intracellular cyclic adenosine monophosphate.* Arzneim Forsch/Drug Res 1995, 45: 18-22.
41. Dallegri, F., Ottonello, L., Bevilacqua, M. *Possible modes of action of nimesulide in controlling neutrophilic inflammation.* Arzneim Forsch/Drug Res 1995, 45: 22-24.
42. Maffei Facino, R., Carini, M., Aldini, G. *Antioxidant activity of nimesulide and its main metabolites.* Drugs 1993, 46 (Suppl. 1): 15-21.
43. Dallegri, F., Ottonello, L., Gatti, F., Guidi, G. *Neutrophil oxidative responses. Cell-directed and scavenging actions of the anti-inflammatory drug nimesulide.* Drug Invest 1991, 3 (Suppl. 2): 71-74.
44. Zentella de Pina, M., Saldana Balmori, Y., Hernandez Tobias, A., Pina, E. *Nonsteroidal antiinflammatory drugs lower ethanol-mediated liver increase in lipids and thiobarbituric acid reactive substances.* Alcohol Clin Exp Res 1993, 17: 1228-1232.
45. Dapino, P., Ottonello, L., Dallegri, F. *The anti-inflammatory drug nimesulide inhibits neutrophil adherence to and migration across monolayers of cytokine-activated endothelial cells.* Respiration 1994, 61: 336-341.
46. Kowanko, I.C., Bates, E.J., Ferrante, A. *Mechanisms of human neutrophil-mediated cartilage damage in vitro: The role of lysosomal enzymes, hydrogen peroxide and hypochlorous acid.* Immunol Cell Biol 1989, 67: 321-329.
47. Pelletier, J.P., Martel Pelletier, J. *Effects of nimesulide and naproxen on the degradation and metalloprotease synthesis of human osteoarthritic cartilage.* Drugs 1993, 46 (Suppl. 1): 34-39.
48. Bevilacqua, M., Magni, E. *Recent contributions to knowledge of the mechanism of action of nimesulide.* Drugs 1993, 46 (Suppl. 1): 40-47.
49. Berti, F., Rossoni, G., Buschi, A., Robuschi, M., Villa, L.M. *Antianaphylactic and antihistaminic activity of the non-steroidal anti-inflammatory compound nimesulide in guinea-pig.* Arzneim Forsch/Drug Res 1990, 40: 1011-1016.
50. Berti, F., Rossoni, G., Buschi, A., Villa, L.M., Robuschi, M., Caratozzolo, O. *Nimesulide, a nonsteroidal anti-inflammatory drug, displays antianaphylactic and antihistaminic activity in guinea-pigs.* Drug Invest 1991, 3 (Suppl. 2): 39-47.
51. Marino, O., Casolaro, V., Meliota, S., Stellato, C., Guidi, G., Marone, G. *Inhibition of histamine release from human Fc epsilon RI(+) cells by nimesulide.* Agents Actions 1992, 36: C311-C314.
52. Casolaro, V., Meliota, S., Marino, O. et al. *Nimesulide, a sulfonanilide nonsteroidal anti-inflammatory drug, inhibits mediator release from human basophils and mast cells.* J Pharmacol Exp Ther 1993, 267: 1375-1385.
53. Rossoni, G., Berti, F., Buschi, A., Villa, L.M., Bella, D.D. *New data concerning the antianaphylactic and antihistaminic activity of nimesulide.* Drugs 1993, 46 (Suppl. 1): 22-28.
54. Berti, F., Rossoni, G., Della Bella, D., Trento, F., Bernareggi, M., Robuschi, M. *Influence of acetaldehyde on airway resistance and plasma exudation in the guinea-pig.* Arzneim Forsch/Drug Res 1994, 44: 1342-1346.
55. Bertora, P., Baldi, G., Vago, T., Chebat, E., Bevilacqua, M., Norbiato, G. *Inhibition of neutrophil respiratory burst by nimesulide. Independence from cytoplasmic pH-regulating mechanisms.* Drug Invest 1991, 3 (Suppl. 2): 91-94.
56. Bianco, S., Robuschi, M., Gambaro, G., Spagnotto, S., Petrigni, G. *Bronchial inflammation and NSAIDs.* Drug Invest 1991, 3 (Suppl. 2): 33-38.
57. Bianco, S., Robuschi, M., Petrigni, G. et al. *Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin.* Drugs 1993, 46 (Suppl. 1): 115-120.
58. Brusasco, V., Crimi, E., Scaricabarozzi, I. *Nimesulide does not interfere with airway responsiveness in allergic asthma.* Drugs 1993, 46 (Suppl. 1): 121-123.
59. Wilhelms, O.H., Linssen, M.J., Lipponer, L., Seilnacht, W. *Nimesulide, indomethacin, BW 755 C, phenidon, mepacrin and nedocromil inhibit the activation of human and rat leucocytes.* Int J Tissue React 1990, 12: 101-106.

60. Ren, B., Zuo, M., Wu Hualan, *Study on mutagenicity of nimesulide in Ames test.* Acta Acad Med Hubei 1994, 15: 7-9.
61. Pochobradsky, M.G., Mele, G., Beretta, A., Montagnani, G. *Post-marketing survey of nimesulide in the short-term treatment of osteoarthritis.* Drugs Exp Clin Res 1991, 17: 197-204.
62. Weissenbach, R. *Clinical trial with nimesulide, a new non-steroid anti-inflammatory agent, in rheumatic pathology.* J Int Med Res 1981, 9: 349-352.
63. Reiner, M. *Nimesulide in the short-term treatment of osteoarthrosis: A pilot study for assessing the minimal effective dose.* J Int Med Res 1982, 10: 92-98.
64. Fossaluzza, V., Montagnani, G. *Efficacy and tolerability of nimesulide in elderly patients with osteoarthritis: Double-blind trial versus naproxen.* J Int Med Res 1989, 17: 295-303.
65. Lucker, P.W., Pawlowski, C., Friederich, I., Faiella, F., Magni, E. *Double-blind, randomised, multi-centre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodalac in patients suffering from osteoarthritis of the knee.* Eur J Rheumatol Inflamm 1994, 14: 29-38.
66. Quattrini, A., Paladin, S. *A double-blind study comparing nimesulide with naproxen in the treatment of osteoarthritis of the hip.* Clin Drug Invest 1995, 10: 139-146.
67. Lecomte, J., Buyse, H., Taymans, J., Monti, T. *Treatment of tendinitis and bursitis: A comparison of nimesulide and naproxen sodium in a double-blind parallel trial.* Eur J Rheumatol Inflamm 1994, 14: 29-32.
68. Dreiser, R.L., Riebenfeld, D. *A double-blind study of the efficacy of nimesulide in the treatment of ankle sprain in comparison with placebo.* Drugs 1993, 46 (Suppl. 1): 183-186.
69. Sad Neto, M. *Treatment of mechanical dorsolumbar pain: A double blind, randomized, comparative study of nimesulide and naproxene.* Rev Bras Med 1995, 52: 220-225.
70. Cattaneo, A., Gibelli, E., Mozzanica, N., Finzi, A.F. *Psoriatic arthritis. The results of a clinical experience with nimesulide.* Spec Oggi Dermatol 1994, 3: 13-16.
71. Riverso, P., Rezzonico, C., Giacometti, B., Bertolini, M. *Nimesulide in the treatment of post-operative pain in minor orthopedic surgery.* Minerva Med 1990, 81: 95-96.
72. Giovannini, M., Zuccotti, G.V., Scaricabarozzi, I., Locatelli, V., Riva, E. *A comparison of nimesulide and placebo in the treatment of minor traumatic soft tissue lesions in children.* Drugs 1993, 46 (Suppl. 1): 212-214.
73. Bourgeois, P., Dreiser, R.L., Lequesne, M.G., Macciocchi, A., Monti, T. *Multi-centre double-blind study to define the most favourable dose of nimesulide in terms of efficacy/safety ratio in the treatment of osteoarthritis.* Eur J Rheumatol Inflamm 1994, 14: 39-50.
74. Milvio, C. *Nimesulide for the treatment of painful inflammatory process in the ear, nose and throat areas: A double-blind controlled study with benzydamine.* J Int Med Res 1984, 12: 327-332.
75. Nouri, M.E. *Nimesulide for treatment of acute inflammation of the upper respiratory tract.* Clin Ther 1984, 6: 142-150.
76. Cadeddu, L., Piragine, F., Puxeddu, P., Scornavacche, V., Sellari Franceschini, S. *Comparison of nimesulide and flurbiprofen in the treatment of non-infectious acute inflammation of the upper respiratory tract.* J Int Med Res 1988, 16: 466-473.
77. Nouri, E., Monti, T. *Nimesulide granules for the treatment of acute inflammation of the ear, nose or throat.* Drugs 1993, 46 (Suppl. 1): 103-106.
78. Ottaviani, A., Mantovani, M., Scaricabarozzi, I. *A multicentre clinical study of nimesulide in inflammatory diseases of the ear, nose and throat.* Drugs 1993, 46 (Suppl. 1): 96-99.
79. Catti, A., Monti, T. *Treatment of infants with acute upper respiratory tract inflammations. A double-blind comparison between nimesulide and paracetamol suppositories.* Clin Trials J 1990, 27: 327-335.
80. Cornaro, G. *A new non-steroidal anti-inflammatory drug in the treatment of inflammations due to parodontal surgery.* Curr Ther Res Clin Exp 1983, 33: 982-989.
81. Pais, J.M., Rosteiro, F.M. *Nimesulide in the short-term treatment of inflammatory process of dental tissues: A double-blind controlled trial against oxyphenbutazone.* J Int Med Res 1983, 11: 149-154.
82. Ragot, J., Giorgi, M., Marinoni, M. et al. *Acute activity of nimesulide in the treatment of pain after oral surgery - Double blind, placebo and mefenamic acid controlled study.* Eur J Clin Res 1994, 5: 39-50.
83. Amodeo, C., De Marco, M., Gambarini, G. *A clinical study of the efficacy and tolerance of nimesulide compared to flurbiprofen and sodium diclofenac in the prevention and treatment of postoperative pain and inflammatory symptoms in dentistry.* Minerva Stomatol 1992, 41: 567-576.
84. Ragot, J.P., Monti, T., Macciocchi, A. *Controlled clinical investigation of acute analgesic activity*

of nimesulide in pain after oral surgery. Drugs 1993, 46 (Suppl. 1): 162-167.
85. Solimei, G.E., Malan, R., Viti, M. et al. *Nimesulide: multicenter clinical study for evaluation of its therapeutic effect in odontostomatology.* Minerva Stomatol 1989, 38: 221-226.
86. Pierleoni, P., Tonelli, P., Scaricabarozzi, I. *A double-blind comparison of nimesulide and ketoprofen in dental surgery.* Drugs 1993, 46 (Suppl. 1): 168-170.
87. Bucci, E., Mignogna, M.D., Scaricabarozzi, I., Bucci, P., Lo Muzio, L., Trezzani, R. *A clinical study of the therapeutic activity and tolerance of nimesulide in a suppository formulation in oral medicine.* Minerva Stomatol 1990, 39: 827-831.
88. De Francesco, G., Palattella, D. *Nimesulide and algo-edematous pathology of the oral cavity.* Dent Cadmos 1990, 58: 56-7, 61.
89. Sofia, M., Molino, A., Mormile, M., Stanziola, A., Scaricabarozzi, I., Carratu, L. *Nimesulide in the treatment of chronic bronchitis.* Drugs 1993, 46 (Suppl. 1): 111-114.
90. Lauriello, G., Giella, D., Berra, A., Vuolo, G., Pacelli, G. *Clinical and spirometric effect of nimesulide in patients suffering from chronic obstructive bronchopneumopathy.* Minerva Pneumol 1994, 33: 13-18.
91. Tomamichel, M., Reiner, M. *Treatment of thrombophlebitis and superficial phlebitis. A comparison of nimesulide and oxyphenbutazone.* Clin Trials J 1983, 20: 148-157.
92. Ferrari, E., Pratesi, C., Scaricabarozzi, I. *A comparison of nimesulide and diclofenac in the treatment of acute superficial thrombophlebitis.* Drugs 1993, 46 (Suppl. 1): 197-199.
93. Agus, G.B., De Angelis, R., Mondani, P., Moia, R. *Double-blind comparison of nimesulide and diclofenac in the treatment of superficial thrombophlebitis with telethermographic assessment.* Drugs 1993, 46 (Suppl. 1): 200-203.
94. Canale, D., Scaricabarozzi, I., Giorgi, P., Turchi, P., Ducci, M., Menchini Fabris, G.F. *Use of a novel non-steroidal anti-inflammatory drug, nimesulide, in the treatment of abacterial prostatovesiculitis.* Andrologia 1993, 25: 163-166.
95. Canale, D., Turchi, P., Giorgi, P.M., Scaricabarozzi, I., Menchini Fabris, G.F. *Treatment of abacterial prostato-vesiculitis with nimesulide.* Drugs 1993, 46 (Suppl. 1): 147-150.
96. Bossemeyer, R. *Comparative study of the efficacy and tolerability of nimesulide versus potassium diclofenac in the treatment of acute pelvic inflammatory disease.* Arq Bras Med 1993, 67: 477-479.
97. Rinaldi, J.F., Cymbalista, N. *Comparative study of the efficacy and tolerability of nimesulide versus sodium diclofenac in the treatment of acute pelvic inflammatory disease.* Arq Bras Med 1994, 68: 229-232.
98. Chiantera, A., Tesauro, R., Di Leo, S., Meli, M.T., Scaricabarozzi, I. *Nimesulide in the treatment of pelvic inflammatory diseases: A multicentre clinical trial conducted in Campania and Sicily.* Drugs 1993, 46 (Suppl. 1): 134-136.
99. Gabbrielli, G., Binazzi, P., Scaricabarozzi, I., Massi, G.B. *Nimesulide in the treatment of mastalgia.* Drugs 1993, 46 (Suppl. 1): 137-139.
100. Pulkkinen, M.O. *The effect of nimesulide on intrauterine pressure in dysmenorrhoeic women.* Drugs Exp Clin Res 1984, 10: 599-606.
101. Rondel, R.K., Eberhardt, R., Koch, J., Schurmann, W. *Treatment of primary essential dysmenorrhoea with nimesulide: A double-blind cross over study.* Curr Ther Res Clin Exp 1984, 35: 123-129.
102. Pulkkinen, M., Monti, T., Macciocchi, A. *Analysis of uterine contractility after administration of the non-steroidal anti-inflammatory drug nimesulide.* Acta Obstet Gynecol Scand 1992, 71: 181-185.
103. Pirhonen, J., Pulkkinen, M. *The effect of nimesulide and naproxen on the uterine and ovarian arterial blood flow velocity. A Doppler study.* Acta Obstet Gynecol Scand 1995, 74: 549-553.
104. Giacovazzo, M., Gallo, M.F., Guidi, V., Rico, R., Scaricabarozzi, I. *Nimesulide in the treatment of menstrual migraine.* Drugs 1993, 46 (Suppl. 1): 140-141.
105. Lecomte, J., Monti, T., Pochobradsky, M.G. *Antipyretic effects of nimesulide in paediatric practice: A double blind study.* Curr Med Res Opin 1991, 12: 296-303.
106. Reiner, M., Massera, E., Magni, E. *Nimesulide in the treatment of fever: A double-blind, cross-over clinical trial.* J Int Med Res 1984, 12: 102-107.
107. Reiner, M., Cereghetti, S., Haeusermann, M., Monti, T. *Antipyretic activity of nimesulide suppositories: Double blind study versus diclofenac and placebo.* Int J Clin Pharmacol Ther Toxicol 1985, 23: 673-677.
108. Cunietti, E., Monti, M., Vigano, A. et al. *A comparison of nimesulide vs paracetamol in the treatment of pyrexia in the elderly.* Drugs 1993, 46 (Suppl. 1): 124-126.
109. Cunietti, E., Monti, M., Vigano, A. et al. *Nimesulide in the treatment of hyperpyrexia in the aged. Double-blind comparison with paracetamol.* Arzneim Forsch/Drug Res 1993, 43: 160-162.
110. Gianiorio, P., Zappa, R., Sacco, O., Fregonese, B., Scaricabarozzi, I., Rossi, G.A. *Antipyretic and anti-inflammatory efficacy of nimesulide vs*

paracetamol in the symptomatic treatment of acute respiratory infections in children. Drugs 1993, 46 (Suppl. 1): 204-207.

111. Pasquale, G., Scaricabarozzi, I., D'Agostino, R., Taborelli, G., Vallarino, R. *An assessment of the efficacy and tolerability of nimesulide vs paracetamol in children after adenotonsillectomy.* Drugs 1993, 46 (Suppl. 1): 234-237.
112. Polidori, G., Titti, G., Pieragostini, P., Comito, A., Scaricabarozzi, I. *A comparison of nimesulide and paracetamol in the treatment of fever due to inflammatory diseases of the upper respiratory tract in children.* Drugs 1993, 46 (Suppl. 1): 231-233.
113. D'Apuzzo, V., Monti, T. *Pilot study of the antipyretic and analgesic activity of nimesulide paediatric suppositories.* Drugs Exp Clin Res 1992, 18: 63-68.
114. Antonelli, A., Cimino, A., Di Girolamo, A. et al. *The treatment of ENT phlogosis: Seaprose S vs. nimesulide.* Acta Otorhinolaryngol Ital 1993, 13 Suppl 39: 1-16.
115. Cimino, A.A.A., Cimino, A., Di Girolamo, A. et al. *Treatment of ENT phlogosis - Seaprose S vs nimesulide.* Acta Otorhinolaryngol Ital 1993, 13: 1-16.
116. Banchini, G., Scaricabarozzi, I., Montecorboli, U. et al. *Double-blind study of nimesulide in divers with inflammatory disorders of the ear, nose and throat.* Drugs 1993, 46 (Suppl. 1): 100-102.
117. Bernasconi, P., Massera, E. *Evaluation of a new pharmaceutical form of nimesulide for the treatment of influenza.* Drugs Exp Clin Res 1985, 11: 739-743.
118. Milvio, C. *Treatment of influenza syndrome: A double-blind controlled trial of nimesulide v. aspirin.* Clin Trials J 1985, 22: 111-117.
119. Stefanoni, G., Saccomanno, F., Scaricabarozzi, I. et al. *Clinical efficacy of nimesulide compared to diclofenac sodium in the prevention and treatment of postoperative pain-inflammation symptomatology.* Minerva Chir 1990, 45: 1469-1475.
120. Ramella, G., Costagli, V., Vetere, M. et al. *Comparison of nimesulide and diclofenac in the prevention and treatment of painful inflammatory postoperative complications of general surgery.* Drugs 1993, 46 (Suppl. 1): 159-161.
121. Zuckermann, M., Panconesi, R., Scaricabarozzi, I., Nava, M.L., Bechi, P. *Clinical efficacy and tolerability of nimesulide compared with naproxen in the treatment of posthaemorrhoidectomy pain and inflammation.* Drugs 1993, 46 (Suppl. 1): 177-179.
122. Scharli, A.F., Brulhart, K., Monti, T. *Pharmacokinetics and therapeutic study with nimesulide suppositories in children with post-operative pain and inflammation.* J Int Med Res 1990, 18: 315-321.
123. Coscarelli, S., Scaricabarozzi, I., Nava, M.L., Alajmo, E. *A comparison of nimesulide and ketoprofen in the prevention and treatment of painful postoperative inflammatory complications of ear, nose and throat surgery.* Drugs 1993, 46 (Suppl. 1): 174-176.
124. Bianchi, A., Campobassi, A., Marchetti, C., Mazzani, E. *Use of nimesulide in orthognathic surgery of the jaws.* Dent Cadmos 1989, 57: 44-8, 51.
125. Scolari, G., Vargiu, G., Scaricabarozzi, I. *The nimesulide treatment of inflammation and post-traumatic pain in maxillofacial surgery. A controlled study versus flurbiprofen.* Minerva Stomatol 1990, 39: 1039-1046.
126. Ferrari Parabita, G., Zanetti, U., Scalvini, F., Rossi, D., Scaricabarozzi, I. *A controlled clinical study of the efficacy and tolerability of nimesulide vs naproxen in maxillo-facial surgery.* Drugs 1993, 46 (Suppl. 1): 171-173.
127. Calligaris, A., Scaricabarozzi, I., Vecchiet, L. *A multicentre double-blind investigation comparing nimesulide and naproxen in the treatment of minor sport injuries.* Drugs 1993, 46 (Suppl. 1): 187-190.
128. Marconcini, C., Sbrana, E., Scaricabarozzi, I. *Efficacy of nimesulide in the prevention of inflammatory complications after laser treatment of ocular diseases.* Drugs 1993, 46 (Suppl. 1): 180-181.
129. Gallucci, M., Toscani, F., Mapelli, A., Cantarelli, A., Veca, G., Scaricabarozzi, I. *Nimesulide in the treatment of advanced cancer pain. Double-blind comparison with naproxen.* Arzneim Forsch/Drug Res 1992, 42: 1028-1030.
130. Toscani, F., Gallucci, M., Scaricabarozzi, I. *Nimesulide in the treatment of advanced cancer pain: Double-blind comparison with naproxen.* Drugs 1993, 46 (Suppl. 1): 156-158.
131. Corli, O., Cozzolino, A., Scaricabarozzi, I. *Nimesulide and diclofenac in the control of cancer-related pain: Comparison between oral and rectal administration.* Drugs 1993, 46 (Suppl. 1): 152-155.
132. Reiner, M. *Nimesulide and antibiotics in the treatment of acute infections of the respiratory tract.* Curr Med Res Opin 1983, 8: 487-492.
133. Malavasi Ganança, M. *Evaluation of nimesulide suppositories in upper respiratory tract infections.* Arq Bras Med 1994, 68: 441-442.
134. Barberi, I., Macchia, A., Spata, N., Scaricabarozzi, I., Nava, M.L. *Double-blind evaluation of nimesulide vs lysine-aspirin in the treatment of*

paediatric acute respiratory tract infections. Drugs 1993, 46 (Suppl. 1): 219-221.

135. Cappella, L., Guerra, A., Laudizi, L., Cavazzuti, G.B. *Efficacy and tolerability of nimesulide and lysine-acetylsalicylate in the treatment of paediatric acute upper respiratory tract inflammation.* Drugs 1993, 46 (Suppl. 1): 222-225.
136. Salzberg, R., Giambonini, S., Maurizio, M., Roulet, D., Zahn, J., Monti, T. *A double-blind comparison of nimesulide and mefenamic acid in the treatment of acute upper respiratory tract infections in children.* Drugs 1993, 46 (Suppl. 1): 208-211.
137. Salmòn Rodriguez, L.E., Arista Viveros, A., Lopez, M., Trujillo, C., Maciel, R., Lujan, M. *Evaluation of the efficacy and safety of nimesulide and naproxen in the symptomatic treatment of upper respiratory tract infections in children. A comparative blind study.* Invest Med Int 1993, 20: 43-54.
138. Salmòn Rodriguez, L.E., Arista Viveros, H.A., Lujan, M.E., Maciel, R.M., Trujillo, C.L., Lopez, E. *Assessment of the efficacy and safety of nimesulide vs naproxen in paediatric patients with respiratory tract infections: A comparative single-blind study.* Drugs 1993, 46 (Suppl. 1): 226-230.
139. Miniti, A., Ferreira Bento, R., Ubirajara Senes, L. *Comparative study with nimesulide drops versus diclofenac resinate in the treatment of pharyngo-tonsillitis in childhood.* Arq Bras Med 1994, 68: 233-241.
140. Pfandner, K. *Nimesulide and antibiotics in the treatment of acute urinary tract infections.* Arzneim Forsch/Drug Res 1984, 34: 77-79.
141. Lotti, T., Mirone, V., Imbimbo, C. et al. *Controlled clinical studies of nimesulide in the treatment of urogenital inflammation.* Drugs 1993, 46 (Suppl. 1): 144-146.
142. Corrado, F., Corrado, G., Fini, M., Tornaselli, V., Garofalo, F., Scaricabarozzi, I. *Efficacy and tolerability of nimesulide in the flogistic affections of the genito-urinary tract.* Minerva Urol Nefrol 1989, 41: 115-119.
143. *Multicenter study with nimesulide drops in pediatrics.* Arq Bras Med 1994, 68: 357-363.
144. Facchini, R., Selva, G., Peretti, G. *Tolerability of nimesulide and ketoprofen in paediatric patients with traumatic or surgical fractures.* Drugs 1993, 46 (Suppl. 1): 238-241.
145. Warrington, S.J., Ravic, M., Dawnay, A. *Renal and general tolerability of repeated doses of nimesulide in normal subjects.* Drugs 1993, 46 (Suppl. 1): 263-269.
146. Fusetti, G., Magni, E., Armandola, M.C. *Tolerability of nimesulide: Epidemiological data.* Drugs 1993, 46 (Suppl. 1): 277-280.
147. Dreiser, R.L., Concas Benevelli, D. *Long term tolerability profile of nimesulide in the treatment of osteoarthritis.* Drugs 1993, 46 (Suppl. 1): 270-274.
148. McCarthy, D.M. *Mechanisms of mucosal injury and healing: The role of non-steroidal anti-inflammatory drugs.* Scand J Gastroenterol 1995, 30 (Suppl. 208): 24-29.
149. Botting, J. *COX-2: Selective inhibitors in clinical trials.* Drug News Perspect 1996, 9: 123-128.
150. Cipollini, F., Mecozzi, V., Altilia, F. *Endoscopic assessment of the effects of nimesulide on the gastric mucosa: Comparison with indomethacin.* Curr Ther Res Clin Exp 1989, 45: 1042-1048.
151. Marini, U., Spotti, D., Magni, E., Monti, T. *Double-blind endoscopic study comparing the effect of nimesulide and placebo on gastric mucosa of dyspeptic subjects.* Drug Invest 1990, 2: 162-166.
152. Marini, U., Spotti, D. *Gastric tolerability of nimesulide: A double-blind comparison of 2 oral dosage regimens and placebo.* Drugs 1993, 46 (Suppl. 1): 249-252.
153. Porto, A., Almeida, H., Cunha, M.J., Macciocchi, A. *Double-blind study evaluating by endoscopy the tolerability of nimesulide and diclofenac on the gastric mucosa in osteoarthritic patients.* Eur J Rheumatol Inflamm 1994, 14: 33-38.
154. Ispano, M., Fontana, A., Scibilia, J., Ortolani, C. *Oral challenge with alternative nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol in patients intolerant to these agents.* Drugs 1993, 46 (Suppl. 1): 253-256.
155. Andri, L., Senna, G., Betteli, C. et al. *Tolerability of nimesulide in aspirin-sensitive patients.* Ann Allergy 1994, 72: 29-32.
156. Lisi, P., Stingeni, L. *Cutaneous adverse reactions to nonsteroidal anti-inflammatory drugs. Etiopathogenic data and review of the literature.* Ann Ital Dermatol Clin Sper 1991, 45: 193-220.
157. Naldi, L., Ferri, C., Locati, F. et al. *Cutaneous reactions to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs.* Dermatology 1993, 186: 164-169.
158. Astarita, C., Franzese, A., Sproviero, S. et al. *The epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. Nimesulide is tolerated by patients with adverse reactions to NSAIDs and modulates in man the skin*

response to histamine and codeine. Recent Prog Med 1992, 83: 567-571.

159. *Cutaneous reactions to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs. Analysis of reports to the spontaneous reporting system of the Gruppo Italiano Studi Epidemiologici in Dermatologia.* Dermatology 1993, 186: 164-169.
160. Perucca, E. *Drug interactions with nimesulide.* Drugs 1993, 46 (Suppl. 1): 79-82.
161. Auteri, A., Bruni, F., Blardi, P. et al. *Clinical study on pharmacological interaction between nimesulide and warfarin.* Int J Clin Pharmacol Res 1991, 11: 267-270.
162. Baggio, E., Maraffi, F., Montalto, C., Nava, M.L., Torti, L., Casciarri, I. *A clinical assessment of the potential for pharmacological interaction between nimesulide and digoxin in patients with heart failure.* Drugs 1993, 46 (Suppl. 1): 91-94.
163. Verhoeven, A.J., Tool, A.T.J., Kuijpers, T.W., Roos, D. *Nimesulide inhibits platelet-activating factor synthesis in activated human neutrophils.* Drugs 1993, 46 (Suppl. 1): 52-58.
164. Bellussi, L., Passali, D. *Treatment of upper airways inflammation with nimesulide.* Drugs 1993, 46 (Suppl. 1): 107-110.
165. Wallace, J.L., Cirino, G. *The development of gastrointestinal-sparing nonsteroidal antiinflammatory drugs.* Trends Pharmacol Sci 1994, 15: 405-406.
166. Roos, D. *The respiratory burst of phagocytic leucocytes.* Drug Invest 1991, 3 (Suppl. 2): 48-53.
167. Miniti, A., Dieb Miziara, I. *Comparative study of nimesulide versus naproxen in patients with pharyngo-tonsillitis.* Arq Bras Med 1991, 65: 511-514.
168. Tanaka, K., Makino, S., Shimotori, T., Aikawa, Y., Inaba, T., Yoshida, C. *Pharmacological studies of the new antiinflammatory agent 3-formylamino - 7 - methylsulfonylamino - 6 - phenoxy - 4H-1-benzopyran-4-one. 2nd Communication: Effect on the arachidonic acid cascades.* Arzneim Forsch/Drug Res 1992, 42: 945-950.
169. Maffei Facino, R., Carini, M., Aldini, G., Saibene, L., Macciocchi, A. *Antioxidant profile of nimesulide, Indomethacin and diclofenac in phosphatidylcholine liposomes (PCL) as membrane model.* Int J Tissue React 1993, 15: 225-234.
170. Tofanetti, O., Casciarri, I., Cipolla, P.V., Cazzulani, P., Omini, C. *Effect of nimesulide on cyclooxygenase activity in rat gastric mucosa and inflammatory exudate.* Med Sci Res 1989, 17: 745-746.
171. Tanaka, K., Shimotori, T., Makino, S. et al. *Pharmacological studies of the new antiinflaminatory agent 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one. 1st communication: Antiinflammatory, analgesic and other related properties.* Arzneim Forsch/Drug Res 1992, 42: 935-944.
172. Bottcher, I., Schweizer, A., Glatt, M., Werner, H. *A sulphonamido-indanone derivative CGP 28237 (ZK 34228), a novel non-steroidal anti-inflammatory agent without gastro-intestinal ulcerogenicity in rats.* Drugs Exp Clin Res 1987, 13: 237-245.
173. Carr, D.P., Henn, R., Green, J.R., Bottcher, I. *Comparison of the systemic inhibition of thromboxane synthesis, anti-inflammatory activity and gastro-intestinal toxicity of non-steroidal anti-inflammatory drugs in the rat.* Agents Actions 1986, 19: 374-375.
174. Ceserani, R., Carboni, L., Germini, M., Mainardi, P., Passoni, A. *Antipyretic and platelet antiaggregating effects of nimesulide.* Drugs 1993, 46 (Suppl. 1): 48-51.
175. Berti, F., Rossoni, G., Robuschi, M., Mandelli, V. *Protective effect of furosemide combined with non-steroidal anti-inflammatory drugs administered by inhalation route on guinea-pigs anaphylaxis model.* Arzneim Forsch/Drug Res 1995, 45: 1098-1102.

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